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(54) Title: ISOQUINOLINE COMPOUND MELANOCORTIN RECEPTOR LIGANDS AND METHODS OF USING SAME

(57) Abstract

The invention relates to melanocortin receptor ligands and methods of using the ligands to alter or regulate the activity of a melanocortin receptor. The invention further relates to tetrahydroisoquinoline aromatic amines that function as melanocortin receptor ligands and as agents for controlling cytokine–regulated physiologic processes and pathologies, and combinatorial libraries thereof.

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ISOQUINOLINE COMPOUND MELANOCORTIN RECEPTOR LIGANDS AND METHODS OF USING SAME

FIELD OF THE INVENTION

The present invention relates generally to the fields of medicinal chemistry and molecular pathology and, more specifically, to novel isoquinoline compounds and their use as melanocortin receptor ligands and as agents for controlling cytokine-regulated physiologic processes and pathologies, as well as combinatorial libraries comprising such compounds.

BACKGROUND INFORMATION

The melanocortin (MC) receptors are a group of cell surface proteins that mediate a variety of physiological effects, including regulation of adrenal gland function such as production of the glucocorticoids cortisol and aldosterone; control of melanocyte growth and pigment production; thermoregulation; immunomodulation; and analgesia. Five distinct MC receptors have been cloned and are expressed in a variety of tissues, including melanocytes, adrenal cortex, brain, gut, placenta, skeletal muscle, lung, spleen, thymus, bone marrow, pituitary, gonads and adipose tissue (Tatro, Neuroimmunomodulation 3:259-284 (1996)). Three MC receptors, MCR-1, MCR-3 and MCR-4, are expressed in brain tissue (Xia et al., Neuroreport 6:2193-2196 (1995)).

A variety of ligands termed melanocortins function as agonists that stimulate the activity of MC receptors. The melanocortins include melanocyte-stimulating hormones (MSH) such as α-MSH, β-MSH and γ-MSH, as well as adrenocorticotropic hormone (ACTH). Individual ligands can bind to multiple MC receptors with differing relative affinities. The variety of ligands and MC receptors with differential tissue-specific expression likely provides the molecular basis for the diverse physiological effects of melanocortins and MC receptors. For example, α-MSH antagonizes the actions of immunological substances such as cytokines and acts to modulate fever, inflammation and immune responses (Catania and Lipton, Annals N. Y. Acad. Sci. 680:412-423 (1993)).

More recently, the role of specific MC receptors in some of the physiological effects described above for MC receptors has been elucidated. For example, MCR-1 is involved in pain and inflammation. MCR-1 mRNA is expressed in neutrophils (Catania et al., Peptides 17:675-679 (1996)). The anti-inflammatory agent α-MSH was found to inhibit migration of neutrophils. Thus, the presence of MCR-1 in neutrophils correlates with the anti-inflammatory activity of α-MSH.

An interesting link of MC receptors to regulation of food intake and obesity has recently been described. The brain MC receptor MCR-4 has been shown to function in the regulation of body weight and food intake. Mice in which MCR-4 has been knocked out exhibit weight gain (Huszar et al., Cell 88:131-141 (1997)). In addition, injection into brain of synthetic peptides that mimic melanocortins and bind to MCR-4 caused suppressed feeding in normal and mutant obese mice (Fan et al.,

Nature 385:165-168 (1997)). These results indicate that the brain MC receptor MCR-4 functions in regulating food intake and body weight.

Due to the varied physiological activities of MC receptors, high affinity ligands of MC receptors could be used to exploit the varied physiological responses of MC receptors by functioning as potential therapeutic agents or as lead compounds for the development of therapeutic agents. Furthermore, due to the effect of MC receptors on the activity of various cytokines, high affinity MC receptor ligands could also be used to regulate cytokine activity.

Thus, there exists a need for ligands that bind to MC receptors with high affinity for use in altering MC receptor activity. The present invention satisfies this need and provides related advantages as well.

SUMMARY OF THE INVENTION

The invention provides melanocortin receptor ligands and methods of using the ligands to alter or regulate the activity of a melanocortin receptor. The invention further relates to tetrahydroisoquinoline aromatic amines that function as melanocortin receptor ligands.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a reaction scheme for synthesis of tetrahydroisoquinoline aromatic amines.

Figure 2 shows inhibition of arachidonic acid induced dermal inflammation with indomethacin

(1 mg/mouse) or TRG 2405-241 (600 μg/mouse) administered orally.

Figure 3 shows inhibition of arachidonic acid induced dermal inflammation with HP 228 (100 μg/mouse) or TRG 2405-241 (300 μg/mouse) administered intraperitoneally.

Figure 4 shows inhibition of arachidonic acid induced dermal inflammation with HP 228, TRG 2405-190, TRG 2405-241, TRG 2405-252 or TRG 2405-253 (100 μg/mouse) administered intraperitoneally.

Figure 5 shows inhibition of arachidonic acid induced dermal inflammation with HP 228 (100 μg/mouse) or with TRG 2409-2 or TRG 2409-14 (100 or 300 μg/mouse) administered intraperitoneally.

Figure 6 shows the effect of HP 228 (5 mg/kg), TRG 2405-190 and TRG 2405-241 (5 mg/kg) on body weight and food consumption in mouse at 18 hr.

Figure 7 shows the effect of HP 228 (5 mg/kg), TRG 2405-252 and TRG 2405-253 (5 mg/kg) on body weight and food consumption in mouse at 9 and 18 hr.

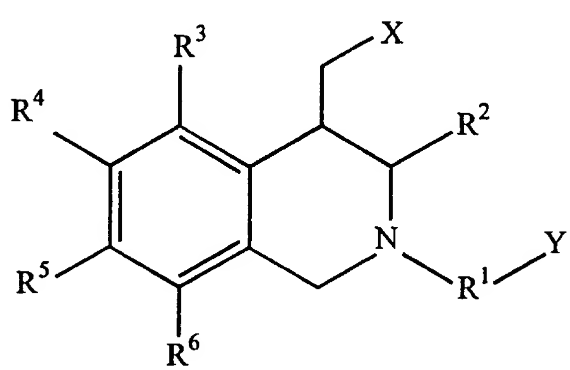
Figure 8 shows the effect of TRG 2411-203 (3.6 mg/kg) compared to HP 228 (1.8 mg/kg) on penile erections in rats.

Figure 9 shows the effect of TRG 2411-203 (3.6 mg/kg) compared to HP 228 (1.8 mg/kg) on yawns and stretches in rats.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides ligands for MC receptors and methods for altering the activity of a MC receptor. The invention also provides MC receptor ligands that are useful for regulating cytokine activity and body weight in an individual. The invention further provides isoquinoline compounds which are MC receptor ligands, as well as combinatorial libraries of such compounds. Isoquinoline compounds of the present invention are more specifically tetrahydroisoquinoline aromatic amines, although other isoquinoline compounds or derivatives thereof can similarly be used as MC receptor ligands.

The invention provides isoquinoline compound MC receptor ligands and combinatorial libraries having the structure:



wherein:

R^1 is a C_1 to C_9 alkylene, C_1 to C_9 substituted alkylene, C_2 to C_9 alkenylene, C_2 to C_9 substituted alkenylene, C_2 to C_9 alkynylene, C_2 to C_9 substituted alkynylene, C_7 to C_{12} phenylalkylene, C_7 to C_{12}

substituted phenylalkylene or a group of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

wherein u is selected from a number 1 to 8; and R^8 is hydrogen atom, C_1 to C_9 alkyl, C_1 to C_9 substituted alkyl, C_7 to C_{12} phenylalkyl or a C_7 to C_{12} substituted phenylalkyl;

R^2 is phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{12} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, a heterocyclic ring or a substituted heterocyclic ring;

R^3, R^4, R^5 and R^6 are, independently, a hydrogen atom, halo, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_2 to C_7 alkenyl, C_2 to C_7 alkynyl, C_1 to C_6 substituted alkyl, C_2 to C_7 substituted alkenyl, C_2 to C_7 substituted alkynyl, C_1 to C_7 alkoxy, C_1 to C_7 acyloxy, C_1 to C_7 acyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, a heterocyclic ring, C_7 to C_{12} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, cyclic C_2 to C_7 alkylene, substituted cyclic C_2 to C_7 alkylene, cyclic C_2 to C_7 heteroalkylene, substituted cyclic C_2 to C_7 heteroalkylene, carboxy, protected carboxy, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, C_1 to C_4

alkylthio, C_1 to C_4 alkylsulfonyl, C_1 to C_4 alkylsulfoxide, phenylthio, substituted phenylthio, phenylsulfoxide, substituted phenylsulfoxide, phenylsulfonyl or substituted phenylsulfonyl;

X is hydroxy, amino, protected amino, an amino acid, (monosubstituted)amino, (disubstituted)amino, aniline, substituted aniline, a heterocyclic ring, a substituted heterocyclic ring, an aminosubstituted heterocyclic ring, or a substituted aminosubstituted heterocyclic ring; and

Y is CH_2NHR^7 or $C(O)NHR^7$, wherein R^7 is a hydrogen atom, C_1 to C_6 alkyl or C_1 to C_6 substituted alkyl.

The invention also provides the above identified substituents with the exception that R^1 is preferably formula $-(CH_2)_u-CH(NHR^8)-$ with the above given u variables and R^8 substituents.

The invention also provides isoquinoline compounds and combinatorial libraries having the above formula, wherein:

R^1 is C_1 to C_9 alkylene or C_1 to C_9 substituted alkylene, or a group of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

wherein u is selected from a number 1 to 8; and R^8 is hydrogen atom, C_1 to C_9 alkyl, C_1 to C_9 substituted alkyl, C_7 to C_{12} phenylalkyl or C_7 to C_{12} substituted phenylalkyl;

R^2 is phenyl, a substituted phenyl, a heterocyclic ring or a substituted heterocyclic ring;

R^3, R^4, R^5 and R^6 are, independently, a hydrogen atom;

X is hydroxy, amino, protected amino, (monosubstituted)amino, (disubstituted)amino, aniline, a substituted aniline, a heterocyclic ring, a substituted heterocyclic ring, an aminosubstituted heterocyclic ring, or a substituted aminosubstituted heterocyclic ring; and

Y is selected from the group consisting of CH_2NHR^7 or $C(O)NHR^7$, wherein R^7 is a hydrogen atom, C_1 to C_6 alkyl or C_1 to C_6 substituted alkyl.

The invention also provides compounds and combinatorial libraries having the substituents identified directly above, with the exception that R^1 is preferably formula $-(CH_2)_u-CH(NHR^8)-$ with the above given u variables and R^8 substituents.

The invention also provides isoquinoline compounds and combinatorial libraries having the above formula, wherein:

R^1 is methylene or the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

wherein u is selected from a number 1 to 6; and R^8 is methyl, ethyl, phenethyl, 2-(N-methylamino)ethyl, 2-aminoethyl, hydroxyethyl, 2-(N-methyl)propyl, 2-(N-methyl)-2-phenyl ethyl, a

reduced and/or modified form of succinic anhydride, methoxyethyl, butyl, cyclohexanemethyl, benzyl, 4-bromophenethyl, 4-methoxyphenethyl, 4-chlorobenzyl, 4-methoxybenzyl, 2-naphthylethyl, or cyclohexylethyl;

R^2 is phenyl, 2-hydroxyphenyl, 1,4-benzodioxan-6-yl, 1-methyl-2-pyrrolyl, 1-naphthyl, 2,3,4-trifluorophenyl, 2,3,5-trichlorophenyl, 2,3-(methylenedioxy)phenyl, 2,3-difluorophenyl, 2,4-dichlorophenyl, 2,6-difluorophenyl, 2-bromophenyl, 2-chloro-5-nitrophenyl, 2-chloro-6-fluorophenyl, 2-aminomethylphenyl, 2-fluorophenyl, 2-imidazolyl, 2-methoxybenzyl, 2-naphthyl, 2-thiophene-yl, 3,4-(methylenedioxy)phenyl, 3,4-dihydroxyphenyl, 3,4-dichlorophenyl, 3,4-difluorophenyl, 3,5-bis(trifluoromethyl)phenyl, 3,5-dihydroxyphenyl, 3,5-dichlorophenyl, 3,5-dimethoxyphenyl, 3,5-dimethyl-4-hydroxyphenyl, 3-(3,4-dichlorophenoxy)phenyl, 3-(4-methoxyphenoxy)phenyl, 3-(trifluoromethyl)phenyl, 3-bromo-4-fluorophenyl, 3-bromophenyl, 3-hydroxymethylphenyl, 3-aminomethylphenyl, 3-fluoro-4-methoxyphenyl, 3-fluorophenyl, 3-hydroxyphenyl, 3-methoxy-4-hydroxy-5-nitrophenyl, 3-methoxyphenyl, 3-methyl-4-methoxyphenyl, 3-methylphenyl, 3-nitro-4-chlorophenyl, 3-nitrophenyl, 3-phenoxyphenyl, 3-pyridinyl, 3-thiophene-yl, 4-(3-dimethylaminopropoxy)phenyl, 4-(dimethylamino)phenyl, 4-hydroxymethylphenyl, 4-(methylthio)phenyl, 4-(trifluoromethyl)phenyl, 4-ethylaminophenyl, 4-methoxyphenyl (p-anisaldehyde), 4-biphenylcarboxaldehyde,

4-bromophenyl, 4-aminomethylphenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-isopropylphenyl, 4-methoxy-1-naphthyl, 4-methylphenyl, 3-hydroxy-4-nitrophenyl, 4-nitrophenyl, 4-phenoxyphenyl, 4-propoxyphenyl, 4-pyridinyl, 3-methoxy-4-hydroxy-5-bromophenyl, 5-methyl-2-thiophene-yl, 5-methyl-2-furyl, 8-hydroxyquinoline-2-yl, 9-ethyl-3-carbazole-yl, 9-formyl-8-hydroxyjulolidin-yl, pyrrole-2-yl, 3-hydroxy-4-methoxyphenyl, 4-methylsulphonylphenyl, 4-methoxy-3-(sulfonic acid, Na)phenyl, 5-bromo-2-furyl, 4-ethoxyphenyl, 4-propoxyphenyl, 4-butoxyphenyl, 4-amylphenyl, 4-propylaminophenyl, 4-butylaminophenyl, 4-pentylaminophenyl, 4-cyclohexylmethylaminophenyl, 4-isobutylaminophenyl, 4-(2-methoxy)-ethylaminophenyl, 4-methoxybenzylaminophenyl, phenethylaminophenyl, 4-methoxyphenethylaminophenyl, 2-(2-norbornyl)-ethylaminophenyl, 3,4-dichlorphenethylaminophenyl, 4-benzylaminophenyl, or 4-p-chlorobenzylaminophenyl;

R^3, R^4, R^5, R^6 are independently a hydrogen atom;

X is anilinyl, N-methylanilinyl, 2-chloroanilinyl, 2-methoxyanilinyl, 3-chloroanilinyl, 3-ethoxyanilinyl, 3-aminophenol, 4-chloroanilinyl, 4-methoxyanilinyl, benzylamino, N-benzylmethylamino, 2-chlorobenzylamino, 2-(trifluoromethyl)benzylamino, 2-hydroxybenzylamino, 3-methoxybenzylamino, 3-(trifluoromethyl)benzylamino, 4-chlorobenzylamino, 4-methoxybenzylamino,

4-(trifluoromethyl)benzylamino, phenethylamino, 2-chlorophenethylamino, 2-methoxyphenethylamino, 3-chlorophenethylamino, 4-methoxyphenthylamino, 3-phenyl-1-propylamino, cyclopentylamino, isopropylamino, cycloheptylamino, N-methylcyclohexylamino, (aminomethyl)cyclohexane, piperidinyl, morpholinyl , 1-aminopiperidinyl, diethylamino, 3-hydroxypropyl, isopropylamino, 2-trimethylaminoethyl chloride, ammonia, or hydroxy; and

Y is CH_2NH_2.

The invention also provides compounds and combinatorial libraries having the substituents identified directly above with the exception that R^1 is preferably formula $-(CH_2)_u-CH(NHR^8)-$ with the above given u variables and R^8 substituents.

The invention further provides isoquinoline compounds and combinatorial libraries having the above formula, wherein:

R^1 is methylene or the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

wherein u is 1, 2 or 4;

R^2 is phenyl, 2-hydroxyphenyl, 1,4-benzodioxan-6-yl, 1-methyl-2-pyrrolyl, 1-naphthyl, 2,3,4-trifluorophenyl, 2,3,5-trichlorophenyl, 2,3-(methylenedioxy)phenyl, 2,3-difluorophenyl,

2,4-dichlorophenyl, 2,6-difluorophenyl, 2-bromophenyl, 2-chloro-5-nitrophenyl, 2-chloro-6-fluorophenyl, 2-cyanophenyl, 2-fluorophenyl, 2-imidazolyl, 2-methoxybenzyl, 2-naphthyl, 2-thiophene-yl, 3,4-(methylenedioxy)phenyl, 3,4-dihydroxyphenyl, 3,4-dichlorophenyl, 3,4-difluorophenyl, 3,5-bis(trifluoromethyl)phenyl, 3,5-dihydroxyphenyl, 3,5-dichlorophenyl, 3,5-dimethoxyphenyl, 3,5-dimethyl-4-hydroxyphenyl, 3-(3,4-dichlorophenoxy)phenyl, 3-(4-methoxyphenoxy)phenyl, 3-(trifluoromethyl)phenyl, 3-bromo-4-fluorophenyl, 3-bromophenyl, 3-hydroxymethylphenyl, 3-aminomethylphenyl, 3-fluoro-4-methoxyphenyl, 3-fluorophenyl, 3-hydroxyphenyl, 3-methoxy-4-hydroxy-5-nitrophenyl, 3-methoxyphenyl, 3-methyl-4-methoxyphenyl, 3-methylphenyl, 3-nitro-4-chlorophenyl, 3-nitrophenyl, 3-phenoxyphenyl, 3-pyridinyl, 3-thiophene-yl, 4-(3-dimethylaminopropoxy)phenyl, 4-(dimethylamino)phenyl, 4-hydroxymethylphenyl, 4-(methylthio)phenyl, 4-(trifluoromethyl)phenyl, 4-ethylaminophenyl, 4-methoxyphenyl, 4-biphenyl, 4-bromophenyl, 4-aminomethylphenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-isopropylphenyl, 4-methoxy-1-naphthyl, 4-methylphenyl, 3-hydroxy-4-nitrophenyl, 4-nitrophenyl, 4-phenoxyphenyl, 4-propoxyphenyl, 4-pyridinyl, 3-methoxy-4-hydroxy-5-bromophenyl, 5-methyl-2-thiophene-yl, 5-methyl-2-furyl, 8-hydroxyquinoline-2-yl, 9-ethyl-3-carbazole-yl, 9-formyl-8-hydroxyjulolidin-yl, pyrrole-2-yl, 3-hydroxy-4-methoxyphenyl, 4-methylsulphonylphenyl, 4-methoxy-3-(sulfonic acid, Na)phenyl or 5-bromo-2-furyl;

R^3, R^4, R^5, R^6 are independently a hydrogen atom;

X is cyclohexylamino;

R^8 is methyl; and

Y is CH_2NH_2.

The invention also provides isoquinoline compounds and combinatorial libraries having the above formula, wherein:

R^1 is methylene or the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

wherein u is 1, 2 or 4;

R^2 is 3-(3,4-dichlorophenoxy)phenyl, 1-methyl-2-pyrrolyl, 3-phenoxyphenyl, 4-phenoxyphenyl, 4-propoxyphenyl, 3-methoxy-4-hydroxy-5-bromophenyl, or 9-ethyl-3-carbazolyl;

R^3, R^4, R^5, R^6 are independently a hydrogen atom;

R^8 is methyl;

X is 2-hydroxybenzyl; and

Y is CH_2NH_2.

The invention additionally provides isoquinoline compounds and combinatorial libraries having the above formula, wherein:

R^1 is methylene or the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

wherein u is 1, 2 or 4;

R^2 is 2,4-dichlorophenyl, 4-biphenyl or 4-ethylaminophenyl;

R^3, R^4, R^5, R^6 are independently a hydrogen atom;

X is anilinyl, N-methylanilinyl, 2-chloroanilinyl, 2-methoxyanilinyl, 3-chloroanilinyl, 3-ethoxyanilinyl, 3-aminophenol, 4-chloroanilinyl, 4-methoxyanilinyl, benzylamino, N-benzylmethylamino, 2-chlorobenzylamino, 2-(trifluoromethyl)benzylamino, 2-hydroxybenzylamino, 3-methoxybenzylamino, 3-(trifluoromethyl)benzylamino, 4-chlorobenzylamino, 4-methoxybenzylamino, 4-(trifluoromethyl)benzylamino, phenethylamino, 2-chlorophenethylamino, 2-methoxyphenethylamino, 3-chlorophenethylamino, 4-methoxyphenthylamino, 3-phenyl-1-propylamino, cyclopentylamino, isopropylamino, cycloheptylamino, N-methylcyclohexylamino, cyclohexylmethylamino, piperidinyl, morpholinyl, 1-aminopiperidinyl, diethylamino, allylamino, isopropylamino,

(2-aminoethyl)-trimethylammonium, ammonium, or hydroxy;

R^8 is methyl; and

Y is CH_2NH_2.

Also provided are isoquinoline compounds and combinatorial libraries having the above formula, wherein:

R^1 is the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

wherein u is 1, 2 or 4;

R^2 is 2,4-dichlorophenyl, 4-biphenyl or 4-ethylaminophenyl;

R^3, R^4, R^5, R^6 are independently a hydrogen atom;

X is cyclohexylamino or 2-hydroxybenzylamino;

R^8 is a hydrogen atom, methyl, phenylethyl, 2-(N-methyl)aminoethyl or 2-aminoethyl; and

Y is CH_2NH_2.

The invention further provides isoquinoline compounds and combinatorial libraries having the above formula, wherein:

R^1 is the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

wherein u is 4;

R^2 is 4-propylaminophenyl, 4-butylaminophenyl, 4-cyclohexylmethylaminophenyl, 4-isobutylaminophenyl, 4-(2-methoxy)-ethylaminophenyl, 4-(4-methoxybenzyl)aminophenyl, 4-phenethylaminophenyl, 4-(4-methoxyphenethyl)aminophenyl, 2-(2-norboranyl)-ethylaminophenyl, 3,4-dichlorophenethylaminophenyl, 4-benzylaminophenyl or 4-p-chlorobenzylaminophenyl;

R^3, R^4, R^5, R^6 are independently a hydrogen atom;

X is cyclohexylamino or 2-hydroxybenzylamino;

R^8 is methyl; and

Y is CH_2NH_2.

The invention also provides isoquinoline compounds and combinatorial libraries having the above formula, wherein:

R^1 is the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

wherein u is 3 or 4;

R^2 is 4-biphenyl, 4-ethylaminophenyl or 4-butylaminophenyl;

R^3, R^4, R^5, R^6 are independently a hydrogen atom;

X is cyclohexylamino, ammonia or phenethylamino;

R^8 is a hydrogen atom, methyl, ethyl, phenylethyl, 2-(N-methyl)aminoethyl, 2-aminoethyl, 2-(N-methyl)aminopropyl, hydroxyethyl, 2-(N-methyl)amino-2-phenyl ethyl, a reduced form of succinic anhydride, methoxyethyl, butyl, cyclohexylmethyl, benzyl, 4-bromophenylethyl, 4-methoxyphenethyl, 4-chlorobenzyl, 4-methoxybenzyl, 2-naphthylethyl or cyclohexylethyl; and

Y is CH_2NH_2.

The invention additionally provides isoquinoline compounds and combinatorial libraries having the above formula, wherein:

R^1 is the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

wherein u is 3 or 4;

R^2 is 4-pentylaminophenyl, 4-ethoxyphenyl, 4-propoxyphenyl, 4-butoxyphenyl or 4-amylphenyl;

R^3, R^4, R^5, R^6 are independently a hydrogen atom;

X is phenethylamino;

R^8 is methyl, phenethyl or benzyl; and
Y is CH_2NH_2.

The invention further provides isoquinoline compounds and combinatorial libraries having the above formula, wherein:

R^1 is the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

wherein u is 3 or 4;

R^2 is 4-biphenyl, 4-ethylaminophenyl or 4-nitrophenyl;

R^3, R^4, R^5, R^6 are independently a hydrogen atom;

X is phenethyl, ammonia or cyclohexylamino;

R^8 is methyl, 2-(N-methyl)aminoethyl or 2-aminoethyl, phenethyl; and

Y is CH_2NH_2.

The invention further provides isoquinoline compounds and combinatorial libraries having the above formula, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

wherein u is 3 and R^8 is a hydrogen atom, phenylethyl, benzyl or 4-isobutyl-α-methylphenylethyl;

R^2 is 2,4-dichlorophenyl, 2-bromophenyl, 3,5-bis(trifluoromethyl)phenyl, 3-phenoxyphenyl, 4-phenoxyphenyl or 4-propoxyphenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is 2-(trifluoromethyl)benzylamino, 2-ethoxybenzylamino, 2-methoxyphenethylamino, 3-chlorophenethylamino, 3-methoxybenzylamino, 4-methoxybenzylamino, 4-methoxyphenethylamino, benzylamino, cycloheptylamino or cyclohexylamino; and

Y is CH_2NH_2.

The invention further provides isoquinoline compounds and combinatorial libraries having the above formula, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

wherein u is 3 or 4 and R^8 is ethyl or cyclohexylethyl;

R^2 is 4-amylphenyl, 4-butoxyphenyl, 4-butylaminophenyl, 4-ethoxyphenyl, 4-ethylphenyl or 4-n-propoxyphenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is ammonia, hydroxy or phenethylamino; and

Y is CH_2NH_2.

In addition, the invention provides isoquinoline compounds and combinatorial libraries having the above formula, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

wherein u is 3 and R^8 is 4-aminobutyl, 4-aminobenzylbutyl, 4-diethylaminobutyl, 4-isopropylaminobutyl, 4-hydroxybutyl, 4-phenethylaminobutyl, 4-piperidinobutyl, 4-t-butylaminobutyl or 4-aminophenylbutyl;

R^2 is 4-ethylaminophenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is ammonia or phenethylamino; and

Y is CH_2NH_2.

The invention also provides isoquinoline compounds and combinatorial libraries having the above formula, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

wherein u is 3 and R^8 is 4-(isopropylamino)-butyl, 4-(benzoamino)-butyl, 4-(diethylamino)-butyl, 4-(phenethylamino)-butyl, 5-(isopropylamino)-(3,4)cyclopropane-pentyl, 5-(benzoamino)-(3,4)cyclopropane-pentyl, 5-(diethylamino)-(3,4)cyclopropane-pentyl, 5-(phenethylamino)-(3,4)cyclopropane-pentyl, 2-amino-2-ethoxy-N-ethylisopropylamino- 2-amino-2-ethoxy-N-ethylbenzyl, 2-amino-2-ethoxy-N-ethyldiethyl, 2-amino-2-ethoxy-N-ethylphenethyl, (2,3)benzyl-4-isopropylamino, (2,3)benzyl-4-benzylamino, (2,3)benzyl-4-diethylamino, (2,3)benzyl-4-phenethylamino, 3-(hydroxy)-5-(isopropylamino)-3-pentyl, 3-(hydroxy)-5-(benzylamino)-3-pentyl, 3-(hydroxy)-5-(diethylamino)-3-pentyl or 3-(hydroxy)-5-(phenethylamino)-3-pentyl;

R^2 is 4-ethylaminophenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is phenethylamino or ammonia; and

Y is CH_2NH_2.

The invention further provides isoquinoline compounds and combinatorial libraries having the above formula, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

u is 4 and R^8 is benzyl, p-methylbenzyl, p-bromobenzyl, p-methoxybenzyl or 4-phenylbenzyl;

R^2 is 3,5-bis(trifluoromethyl)phenyl or 3-(trifluoromethyl)phenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is phenethylamino, tyramino, 2-(4-methoxyphenyl)ethylamino, 3,4-dimethoxyphenylethylamino, 4-ethoxyphenethylamino, 4-phenoxyphenethylamino, 2-(4-chlorophenyl)ethylamino or 2-(3-methoxyphenyl)ethylamino; and

Y is CH_2NH_2.

Additionally, the invention provides isoquinoline compounds and combinatorial libraries having the above formula, wherein:

R^1 is 5-(2-aminoethylamino)pentyl;

R^2 is p-(N-ethylamino)benzyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is 2-methoxybenzylamino, 4-methoxybenzylamino, cyclohexylamino, phenethylamino or ammonia; and

Y is CH_2NH_2.

Moreover, the invention provides isoquinoline compounds and combinatorial libraries having the above formula, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

wherein u is 3 or 4 and R^8 is pentyl, 4-phenoxybutyl or 4-hydroxypentyl;

R^2 is p-(N-ethylamino)benzyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is phenethylamino or ammonia; and

Y is CH_2NH_2.

Furthermore, the invention provides isoquinoline compounds and combinatorial libraries having the above formula, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

wherein u is 4 and R^8 is (α,α,α-trifluoro-p-tolyl)ethyl, 3-(4-methoxyphenyl)propyl, 4-biphenylmethyl, 4-biphenylethyl, 4-chlorophenylethyl, 4-phenoxybutyl, butyl, glycolyl, a hydrogen atom, hydrocinnamylmethyl, isobutylmethyl, methyl, p-methoxybenzyl, 4-hydroxybutyl or 2-(trimethyl)ethyl;

R^2 is 4-propoxyphenyl, 4-amylphenyl or 3,5-bistrifluoromethylphenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is ammonia or cycloheptylamino; and

Y is CH_2NH_2.

The invention additionally provides isoquinoline compounds and combinatorial libraries having the above formula, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

wherein u is 4 and R^8 is methyl or phenethyl;

R^2 is 4-propoxyphenyl, 4-amylphenyl or 3,5-bistrifluoromethylphenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is 4-chlorobenzylamino, 4-methoxybenzylamino, 4-methoxyphenethylamino, phenylamino, benzylamino, cyclohexanemethylamino, cyclohexylamino, cyclooctylamino, cyclopentylamino, diethylamino, ethanolamino, isopropylamino, morpholino, n-methylanilino, n-methylcyclohexylamino, hydroxy, p-anisidino, phenethylamino, piperidino or t-butylamino; and

Y is CH_2NH_2.

The invention also provides isoquinoline compounds and combinatorial libraries having the above formula, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

wherein u is 4 and R^8 is (α,α,α-trifluoro-p-tolyl)ethyl, 1-adamantaneethyl, 3-(4-methoxyphenyl)propyl, 4-phenylbenzyl, 4-phenylphenethyl, 4-chlorophenethyl, 4-imidazolemethyl, 4-methoxyphenyethyl, 4-phenoxypentyl, α,α,α-trifluoro-p-toluylethyl, ethyl, benzyl, butyl, glycolyl, hydrocinnamylmethyl, isobutylmethyl, p-methoxybenzyl, phenethyl, 4-hydroxybutyl or 2-(trimethyl)ethyl;

R^2 is 4-propoxyphenyl, 4-amylphenyl or 3,5-bistrifluoromethylphenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is ammonia or cycloheptylamino; and

Y is CH_2NH_2.

The invention further provides an isoquinoline compound having the above formula, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is the number 4; and R^8 is methyl; R^2 is 2,4-dichlorophenyl; R^3, R^4, R^5, R^6 are independently a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2. This isoquinoline compound is designated TRG 2405#190.

The invention also provides an isoquinoline compound having the above formula, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is the number 4; and R^8 is methyl; R^2 is 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are independently a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2. This isoquinoline compound is designated TRG 2405#239.

The invention additionally provides provides an isoquinoline compound having the above formula, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is the number 4; and R^8 is methyl; R^2 is 4-biphenyl; R^3, R^4, R^5, R^6 are independently a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2. This isoquinoline compound is designated TRG 2405#241.

The invention further provides an isoquinoline compound having the above formula, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is the number 4; and R^8 is methyl; R^2 is 4-phenoxyphenyl; R^3, R^4, R^5, R^6 are independently a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2. This isoquinoline compound is designated TRG 2405#252.

The invention also provides an isoquinoline compound having the above formula, wherein R^1 is

$-(CH_2)_u-CH(NHR^8)-$; u is the number 4; and R^8 is methyl; R^2 is 4-propoxyphenyl; R^3, R^4, R^5, R^6 are independently a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2. This isoquinoline compound is designated TRG 2405#253.

The invention additionally provides an isoquinoline compound having the above formula, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is the number 4; and R^8 is methyl; R^2 is 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are independently a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2. This isoquinoline compound is designated TRG 2408#30.

Also provided is an isoquinoline compound having the above formula, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is the number 3; and R^8 is 2-phenylethyl; R^2 is 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are independently a hydrogen atom; X is 2-hydroxybenzylamino; and Y is CH_2NH_2. This isoquinoline compound is designated TRG 2408#57.

Additionally provided is an isoquinoline compound having the above formula, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is the number 3; and R^8 is 2-phenylethyl; R^2 is 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are independently a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2. This isoquinoline compound is designated TRG 2408#62.

The invention further provides an isoquinoline compound having the above formula, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is the number 4; and R^8 is methyl; R^2 is 4-butylaminophenyl; R^3, R^4, R^5, R^6 are independently a hydrogen atom; X is 2-hydroxybenzylamino; and Y is CH_2NH_2. This isoquinoline compound is designated TRG 2409#2.

The invention also provides an isoquinoline compound having the above formula, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is the number 4; and R^8 is methyl; R^2 is 4-butylaminophenyl; R^3, R^4, R^5, R^6 are independently a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2. This isoquinoline compound is designated TRG 2409#14.

The invention additionally provides an isoquinoline compound having the above formula, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is the number 4; and R^8 is 2-(N-methyl)aminoethyl; R^2 is 4-biphenyl; R^3, R^4, R^5, R^6 are independently a hydrogen atom; X is amino; and Y is CH_2NH_2. This isoquinoline compound is designated TRG 2411#26.

The invention further provides an isoquinoline compound having the above formula, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is the number 4; and R^8 is butyl; R^2 is 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are independently a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2. This isoquinoline compound is designated TRG 2411#50.

Further provided is an isoquinoline compound having the above formula, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is the number 4; and R8 is ethyl; R^2 is 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are independently a hydrogen atom; X is amino; and Y is CH_2NH_2. This isoquinoline compound is designated TRG 2411#60.

The invention also provides an isoquinoline compound having the above formula, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is the number 4; and R^8 is 2-cyclohexylethyl; R^2 is 4-butylaminophenyl; R^3, R^4, R^5, R^6 are independently a hydrogen atom; X is amino; and Y is

CH_2NH_2. This isoquinoline compound is designated TRG 2411#111.

The invention additionally provides an isoquinoline compound having the above formula, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is the number 3; and R^8 is 2-cyclohexylethyl; R^2 is 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are independently a hydrogen atom; X is amino; and Y is CH_2NH_2. This isoquinoline compound is designated TRG 2411#186.

The invention additionally provides an isoquinoline compound having the above formula, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 3; and R^8 is 4-hydroxybutyl; R^2 is 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is 2-phenethylamino; and Y is CH_2NH_2.

The invention additionally provides an isoquinoline compound having the above formula, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is 2-phenethyl; R^2 is 4-propoxyphenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is cycloheptylamino; and Y is CH_2NH_2.

The invention also provides an isoquinoline compound having the above formula, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is ethyl; R^2 is 4-ethoxyphenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is amino; and Y is CH_2NH_2.

The invention also provides an isoquinoline compound having the above formula, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is ethyl; R^2 is 4-propoxyphenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is amino; and Y is CH_2NH_2.

In addition, the invention also provides an isoquinoline compound having the above formula, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is ethyl; R^2 is 4-n-butoxyphenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is amino; and Y is CH_2NH_2.

Moreover, the invention also provides an isoquinoline compound having the above formula, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is ethyl; R^2 is 4-n-pentylphenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is amino; and Y is CH_2NH_2.

Furthermore, the invention also provides an isoquinoline compound having the above formula, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 3; and R^8 is 4-hydroxybutyl; R^2 is 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is amino; and Y is CH_2NH_2.

The invention further provides an isoquinoline compound having the above formula, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 3; and R^8 is pentyl; R^2 is 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is 2-phenethylamino; and Y is CH_2NH_2.

The invention further provides an isoquinoline compound having the above formula, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is 4-hydroxybutyl; R^2 is 4-pentylphenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is amino; and Y is CH_2NH_2.

In the above formula, the R^1-Y substituents are such that Y is always bonded to the 1-position of the R^1 radical. All naming hereinafter reflects this positioning between the two substituents.

Unless otherwise indicated, in the above formula the stereochemistry of chiral centers associated with the R^1 through R^8 groups can independently be in the R or S configuration, or a mixture of the two.

In the above formula, the term "ene" (such as alylene) denotes that the "ene" group connects together two separate additional groups.

In the above formula, the term "alkyl" (such as C_1 to C_9 alkyl or C_1 to C_6 alkyl) denotes such radicals as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, tert-amyl, hexyl and the like up to chains of nine carbon atoms. Preferably, the compounds have C_1 to C_8, more preferably C_1 to C_6 and even more preferably C_1 to C_3 carbon chains. Most preferred is methyl.

The term "alkenyl" (such as C_2 to C_9 alkenyl or C_2 to C_7 alkenyl) denotes such radicals as vinyl, allyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl, as well as dienes and trienes of straight and branched chains.

The term "alkynyl" (such as C_2 to C_9 alkynyl or C_2 to C_7 alkynyl) denotes such radicals as ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, as well as di- and tri-ynes of straight and branched chains.

The terms "substituted alkyl," "substituted alkenyl," and "substituted alkynyl," denote that the above alkyl, alkenyl and alkynyl groups are substituted by one or more, and preferably one or two, halogen, hydroxy, protected hydroxy, oxo, protected oxo,

cyclohexyl, naphthyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, guanidino, heterocyclic ring, substituted heterocyclic ring, imidazolyl, indolyl, pyrrolidinyl, C_1 to C_7 alkoxy, C_1 to C_7 acyl, C_1 to C_7 acyloxy, nitro, C_1 to C_7 alkyl ester, carboxy, protected carboxy, carbamoyl, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N,N-di(C_1 to C_6 alkyl)carboxamide, cyano, methylsulfonylamino, thio, C_1 to C_4 alkylthio or C_1 to C_4 alkyl sulfonyl groups. The substituted alkyl groups may be substituted once or more, and preferably once or twice, with the same or with different substituents.

Examples of the above substituted alkyl groups include the 2-oxo-prop-1-yl, 3-oxo-but-1-yl, cyanomethyl, nitromethyl, chloromethyl, hydroxymethyl, tetrahydropyranyloxymethyl, trityloxymethyl, propionyloxymethyl, amino, methylamino, aminomethyl, dimethylamino, carboxymethyl, allyloxycarbonylmethyl, allyloxycarbonylaminomethyl, methoxymethyl, ethoxymethyl, t-butoxymethyl, acetoxymethyl, chloromethyl, bromomethyl, iodomethyl, trifluoromethyl, 6-hydroxyhexyl, 2,4-dichloro(n-butyl), 2-aminopropyl, chloroethyl, bromoethyl, fluoroethyl, iodoethyl, chloropropyl, bromopropyl, fluoropropyl, iodopropyl and the like.

Examples of the above substituted alkenyl groups include styrenyl, 3-chloro-propen-1-yl, 3-chloro-buten-1-yl, 3-methoxy-propen-2-yl, 3-phenyl-buten-2-yl, 1-cyano-buten-3-yl and the like. The geometrical isomerism is not critical, and all geometrical isomers for a given substituted alkenyl can be used.

Examples of the above substituted alkynyl groups include phenylacetylen-1-yl, 1-phenyl-2-propyn-1-yl and the like.

The term "oxo" denotes a carbon atom bonded to two additional carbon atoms substituted with an oxygen atom doubly bonded to the carbon atom, thereby forming a ketone moiety.

The term "protected oxo" denotes a carbon atom bonded to two additional carbon atoms substituted with two alkoxy groups or twice bonded to a substituted diol moiety, thereby forming an acyclic or cyclic ketal moiety.

The term "C_1 to C_7 alkoxy" as used herein denotes groups such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, t-butoxy and like groups. A preferred alkoxy is methoxy.

The term "C_1 to C_7 acyloxy" denotes herein groups such as formyloxy, acetoxy, propionyloxy, butyryloxy, pentanoyloxy, hexanoyloxy, heptanoyloxy and the like.

Similarly, the term "C_1 to C_7 acyl" encompasses groups such as formyl, acetyl, propionyl, butyryl, pentanoyl, pivaloyl, hexanoyl, heptanoyl, benzoyl and the like. Preferred acyl groups are acetyl and benzoyl.

The term "C_3 to C_7 cycloalkyl" includes the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl rings. The substituent term "C_3 to C_7 substituted cycloalkyl" indicates the above cycloalkyl rings substituted by one or two halogen, hydroxy,

protected hydroxy, C_1 to C_6 alkyl, C_1 to C_7 alkoxy, oxo, protected oxo, (monosubstituted)amino, (disubstituted)amino, trifluoromethyl, carboxy, protected carboxy, phenyl, substituted phenyl, amino, or protected amino groups.

The term "C_5 to C_7 cycloalkenyl" indicates a 1,2, or 3-cyclopentenyl ring, a 1,2,3 or 4-cyclohexenyl ring or a 1,2,3,4 or 5-cycloheptenyl ring, while the term "substituted C_5 to C_7 cycloalkenyl" denotes the above C_5 to C_7 cycloalkenyl rings substituted by a C_1 to C_6 alkyl radical, halogen, hydroxy, protected hydroxy, C_1 to C_7 alkoxy, trifluoromethyl, carboxy, protected carboxy, oxo, protected oxo, (monosubstituted)amino, protected (monosubstituted)amino (disubstituted)amino, phenyl, substituted phenyl, amino, or protected amino.

The term "heterocyclic ring" denotes optionally substituted five-membered or six-membered rings that have 1 to 4 heteroatoms, such as oxygen, sulfur and/or nitrogen, in particular nitrogen, either alone or in conjunction with sulfur or oxygen ring atoms. These five-membered or six-membered rings may be saturated, fully saturated or partially unsaturated, with fully saturated rings being preferred. An "amino-substituted heterocyclic ring" means any one of the above-described heterocyclic rings is substituted with at least one amino group. Preferred heterocyclic rings include morpholino, piperidinyl, piperazinyl, tetrahydrofurano, pyrrolo, and tetrahydrothiophen-yl.

The term "substituted heterocyclic ring" means the above-described heterocyclic ring is substituted with, for example, one or more, and preferably one or two, substituents which are the same or different which

substituents can be halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_7 alkoxy, C_1 to C_7 acyl, C_1 to C_7 acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N, N-di(C_1 to C_6 alkyl), trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino or N-(phenylsulfonyl)amino groups. The term "aminosubstituted heterocyclic ring" is a heterocyclic ring substituted with at least one amino group and the term "substituted aminosubstituted heterocyclic ring is an aminosubstituted heterocyclic ring substituted with one or more of the above identified substituents for a substituted heterocyclic ring.

The abbreviation "Ar" stands for an aryl group. Aryl groups which can be used with present invention include phenyl, substituted phenyl, as defined above, heteroaryl, and substituted heteroaryl. The term "heteroaryl" means a heterocyclic aromatic derivative which is a five-membered or six-membered ring system having from 1 to 4 heteroatoms, such as oxygen, sulfur and/or nitrogen, in particular nitrogen, either alone or in conjunction with sulfur or oxygen ring atoms. Examples of heteroaryls include pyridinyl, pyrimidinyl, and pyrazinyl, pyridazinyl, pyrrolo, furano, oxazolo, isoxazolo, thiazolo and the like.

The term "substituted heteroaryl" means the above-described heteroaryl is substituted with, for example, one or more, and preferably one or two, substituents which are the same or different which

substituents can be halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_7 alkoxy, C_1 to C_7 acyl, C_1 to C_7 acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N, N-di(C_1 to C_6 alkyl) , trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino or N-(phenylsulfonyl)amino groups.

The term "C_7 to C_{12} phenylalkyl" denotes a C_1 to C_6 alkyl group substituted at any position by a phenyl ring. Examples of such a group include benzyl, 2-phenylethyl, 3-phenyl(n-propyl), 4-phenylhexyl, 3-phenyl(n-amyl), 3-phenyl(sec-butyl) and the like. Preferred C_7 to C_{12} phenylalkyl groups are the benzyl and the phenylethyl groups.

The term "C_7 to C_{12} substituted phenylalkyl" denotes a C_7 to C_{12} phenylalkyl group substituted on the C_1 to C_6 alkyl portion with one or more, and preferably one or two, groups chosen from halogen, hydroxy, protected hydroxy, oxo, protected oxo, amino, protected amino, monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, guanidino, heterocyclic ring, substituted heterocyclic ring, C_1 to C_7 alkoxy, C_1 to C_7 acyl, C_1 to C_7 acyloxy, nitro, carboxy, protected carboxy, carbamoyl, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N, N-(C_1 to C_6 dialkyl)carboxamide, cyano, N-(C_1 to C_6 alkylsulfonyl)amino, thiol, C_1 to C_4 alkylthio, C_1 to C_4 alkylsulfonyl groups; and/or the phenyl group may be substituted with one or more, and

preferably one or two, substituents chosen from halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_7 alkoxy, C_1 to C_7 acyl, C_1 to C_7 acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl) carboxamide, protected N-(C_1 to C_6 alkyl) carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino, N-(phenylsulfonyl)amino or a phenyl group, substituted or unsubstituted, for a resulting biphenyl group. The substituted alkyl or phenyl groups may be substituted with one or more, and preferably one or two, substituents which can be the same or different.

Examples of the term "C_7 to C_{12} substituted phenylalkyl" include groups such as 2-phenyl-1-chloroethyl, 2-(4-methoxyphenyl)ethyl, 4-(2,6-dihydroxy phenyl)-n-hexyl, 2-(5-cyano-3-methoxyphenyl)-n-pentyl, 3-(2,6-dimethylphenyl)-n-propyl, 4-chloro-3-aminobenzyl, 6-(4-methoxyphenyl)-3-carboxy(n-hexyl), 5-(4-aminomethylphenyl)-3-(aminomethyl)-n-pentyl, 5-phenyl-3-oxo-n-pent-1-yl and the like.

The term "substituted phenyl" specifies a phenyl group substituted with one or more, and preferably one or two, moieties chosen from the groups consisting of halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_7 alkoxy, C_1 to C_7 acyl, C_1 to C_7 acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected

(monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino, N-(phenylsulfonyl)amino or phenyl, substituted or unsubstituted, such that, for example, a biphenyl results.

Examples of the term "substituted phenyl" include a mono- or di(halo)phenyl group such as 2, 3 or 4-chlorophenyl, 2,6-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 2, 3 or 4-bromophenyl, 3,4-dibromophenyl, 3-chloro-4-fluorophenyl, 2, 3 or 4-fluorophenyl and the like; a mono or di(hydroxy)phenyl group such as 2, 3 or 4-hydroxyphenyl, 2,4-dihydroxyphenyl, the protected-hydroxy derivatives thereof and the like; a nitrophenyl group such as 2, 3 or 4-nitrophenyl; a cyanophenyl group, for example, 2, 3 or 4-cyanophenyl; a mono- or di(alkyl)phenyl group such as 2, 3 or 4-methylphenyl, 2,4-dimethylphenyl, 2, 3 or 4-(iso-propyl)phenyl, 2, 3 or 4-ethylphenyl, 2, 3 or 4-(n-propyl)phenyl and the like; a mono or di(alkoxyl)phenyl group, for example, 2,6-dimethoxyphenyl, 2, 3 or 4-methoxyphenyl, 2, 3 or 4-ethoxyphenyl, 2, 3 or 4-(isopropoxy)phenyl, 2, 3 or 4-(t-butoxy)phenyl, 3-ethoxy-4-methoxyphenyl and the like; 2, 3 or 4-trifluoromethylphenyl; a mono- or dicarboxyphenyl or (protected carboxy)phenyl group such as 2, 3 or 4-carboxyphenyl or 2,4-di(protected carboxy)phenyl; a mono-or di(hydroxymethyl)phenyl or (protected hydroxymethyl)phenyl such as 2, 3, or 4-(protected hydroxymethyl)phenyl or 3,4-di(hydroxymethyl)phenyl; a mono- or di(aminomethyl)phenyl or (protected aminomethyl)phenyl

such as 2, 3 or 4-(aminomethyl)phenyl or 2,4-(protected aminomethyl)phenyl; or a mono- or di(N-(methylsulfonylamino))phenyl such as 2, 3 or 4-(N-(methylsulfonylamino))phenyl. Also, the term "substituted phenyl" represents disubstituted phenyl groups wherein the substituents are different, for example, 3-methyl-4-hydroxyphenyl, 3-chloro-4-hydroxyphenyl, 2-methoxy-4-bromophenyl, 4-ethyl-2-hydroxyphenyl, 3-hydroxy-4-nitrophenyl, 2-hydroxy 4-chlorophenyl and the like.

Phenylthio, phenyl sulfoxide, and phenylsulfonyl compounds are known in the art and these terms have their art recognized definition. By "substituted phenylthio," "substituted phenyl sulfoxide," and "substituted phenylsulfonyl" is meant that the phenyl can be substituted as described above in relation to "substituted phenyl."

The term "substituted aniline" specifies an aniline group substituted with one or more, and preferably one or two, moieties chosen from the groups consisting of halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_7 alkoxy, C_1 to C_7 acyl, C_1 to C_7 acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino and N-(phenylsulfonyl)amino.

Examples of substituted aniline include 2-fluoroanilinyl, 3-fluoroanilinyl, 4-fluoroanilinyl, 2-chloroanilinyl, 3-chloroanilinyl, 4-chloroanilinyl, 2-bromoanilinyl, 3-bromoanilinyl, 4-bromoanilinyl, 2-methoxyanilinyl, 3-methoxyanilinyl, 4-methoxyanilinyl, 2-hydroxyanilinyl, 3-hydroxyanilinyl, 4-hydroxyanilinyl, 2-carboethoxyanilinyl, 3-carboethoxyanilinyl, 4-carboethoxyanilinyl, 2-trifluoromethylanilinyl, 3-trifluoromethylanilinyl, 4-trifluoromethylanilinyl, 2-dimethylaminoanilinyl, 3-dimethylaminoanilinyl, 4-dimethylaminoanilinyl, 2-phenoxyanilinyl, 3-phenoxyanilinyl, 4-phenoxyanilinyl, 3,4-methylenedioxyanilinyl, 2,3-methylenedioxyanilinyl, 2,3-difluoroanilinyl, 2,3-dibromoanilinyl, 3,4-dibromoanilinyl, 2,3-dimethoxyanilinyl, 3,4-dimethoxyanilinyl, 1-amino-5,6,7,8-tetrahydronaphthyl, 2-hydroxy-3-amino-5,6,7,8-tetrahydronaphthyl, 2-aminonaphthyl, 1-amino-4-chloronaphthyl, 1-amino-4-bromonaphthyl, 5-amino-1-hydroxynaphthyl, 1-amino-2-hydroxynaphthyl, 5-aminoindanyl, 1-aminofluorenyl, 2-aminofluorenyl and N-methylanilinyl.

The term "substituted naphthyl" specifies a naphthyl group substituted with one or more, and preferably one or two, moieties either on the same ring or on different rings chosen from the groups consisting of halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_7 alkoxy, C_1 to C_7 acyl, C_1 to C_7 acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6

alkyl)carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino or N-(phenylsulfonyl)amino.

Examples of the term "substituted naphthyl" include a mono or di(halo)naphthyl group such as 1, 2, 3, 4, 5, 6, 7 or 8-chloronaphthyl, 2, 6-dichloronaphthyl, 2, 5-dichloronaphthyl, 3, 4-dichloronaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-bromonaphthyl, 3, 4-dibromonaphthyl, 3-chloro-4-fluoronaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-fluoronaphthyl and the like; a mono or di(hydroxy)naphthyl group such as 1, 2, 3, 4, 5, 6, 7 or 8-hydroxynaphthyl, 2, 4-dihydroxynaphthyl, the protected-hydroxy derivatives thereof and the like; a nitronaphthyl group such as 3- or 4-nitronaphthyl; a cyanonaphthyl group, for example, 1, 2, 3, 4, 5, 6, 7 or 8-cyanonaphthyl; a mono- or di(alkyl)naphthyl group such as 2, 3, 4, 5, 6, 7 or 8-methylnaphthyl, 1, 2, 4-dimethylnaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-(isopropyl)naphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-ethylnaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-(n-propyl)naphthyl and the like; a mono or di(alkoxy)naphthyl group, for example, 2, 6-dimethoxynaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-methoxynaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-ethoxynaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-(isopropoxy)naphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-(t-butoxy)naphthyl, 3-ethoxy-4-methoxynaphthyl and the like; 1, 2, 3, 4, 5, 6, 7 or 8-trifluoromethylnaphthyl; a mono- or dicarboxynaphthyl or (protected carboxy)naphthyl group such as 1, 2, 3, 4, 5, 6, 7 or 8-carboxynaphthyl or 2, 4-di(-protected carboxy)naphthyl; a mono-or di(hydroxymethyl)naphthyl or (protected hydroxymethyl)naphthyl such as 1, 2, 3, 4, 5, 6, 7 or 8-(protected hydroxymethyl)naphthyl or 3,4-di(hydroxymethyl)naphthyl; a mono- or

di(amino)naphthyl or (protected amino)naphthyl such as 1, 2, 3, 4, 5, 6, 7 or 8-(amino)naphthyl or 2, 4-(protected amino)-naphthyl, a mono- or di(aminomethyl)naphthyl or (protected aminomethyl)naphthyl such as 2, 3, or 4-(aminomethyl)naphthyl or 2,4-(protected aminomethyl)-naphthyl; or a mono- or di-(N-methylsulfonylamino) naphthyl such as 1, 2, 3, 4, 5, 6, 7 or 8-(N-methylsulfonylamino)naphthyl. Also, the term "substituted naphthyl" represents disubstituted naphthyl groups wherein the substituents are different, for example, 3-methyl-4-hydroxynaphth-1-yl, 3-chloro-4-hydroxynaphth-2-yl, 2-methoxy-4-bromonaphth-1-yl, 4-ethyl-2-hydroxynaphth-1-yl, 3-hydroxy-4-nitronaphth-2-yl, 2-hydroxy-4-chloronaphth-1-yl, 2-methoxy-7-bromonaphth-1-yl, 4-ethyl-5-hydroxynaphth-2-yl, 3-hydroxy-8-nitronaphth-2-yl, 2-hydroxy-5-chloronaphth-1-yl and the like.

The terms "halo" and "halogen" refer to the fluoro, chloro, bromo or iodo groups. There can be one or more halogen, which are the same or different. Preferred halogens are bromo, fluoro and chloro.

The term "(monosubstituted)amino" refers to an amino group with one substituent chosen from the group consisting of phenyl, substituted phenyl, C_1 to C_6 alkyl, C_1 to C_6 substituted alkyl, C_1 to C_7 acyl, C_2 to C_7 alkenyl, C_2 to C_7 substituted alkenyl, C_2 to C_7 alkynyl, C_2 to C_7 substitued alkynyl, C_7 to C_{12} phenylalkyl, C_7 to C_{12} substituted phenylalkyl and heterocyclic ring. The (monosubstituted)amino can additionally have an amino-

protecting group as encompassed by the term "protected (monosubstituted)amino."

Examples of the term (monosubstituted)amino include methylamino, ethylamino, cyclohexylamino, cyclohexylmethyl, cyclohexylethyl, cyclopentylamino, anilinyl, 2-methoxyanilinyl, benzylamino, 2-hydroxybenzylamino, phenethylamino, 2-methoxyphenethylamino and the like.

The term "(disubstituted)amino" refers to amino groups with two substituents chosen from the group consisting of phenyl, substituted phenyl, C_1 to C_6 alkyl, C_1 to C_6 substituted alkyl, C_1 to C_7 acyl, C_2 to C_7 alkenyl, C_2 to C_7 alkynyl, C_7 to C_{12} phenylalkyl, and C_7 to C_{12} substituted phenylalkyl. The two substituents can be the same or different.

The term "amino-protecting group" as used herein refers to substituents of the amino group commonly employed to block or protect the amino functionality while reacting other functional groups of the molecule. The term "protected (monosubstituted)amino" means there is an amino-protecting group on the monosubstituted amino nitrogen atom. In addition, the term "protected carboxamide" means there is an amino-protecting group on the carboxamide nitrogen.

Examples of such amino-protecting groups include the formyl ("For") group, the trityl group, the phthalimido group, the trichloroacetyl group, the chloroacetyl, bromoacetyl, and iodoacetyl groups, urethane-type blocking groups, such as t-butoxycarbonyl ("Boc"), 2-(4-biphenylyl)propyl-2-oxycarbonyl ("Bpoc"), 2-phenylpropyl-2-oxycarbonyl ("Poc"), 2-(4-xenyl)isopropoxycarbonyl, 1,1-diphenylethyl-1-oxycarbonyl,

1,1-diphenylpropyl-1-oxycarbonyl, 2-(3,5-dimethoxyphenyl)propyl-2-oxycarbonyl ("Ddz"), 2-(*p*-toluyl)propyl-2-oxycarbonyl, cyclopentanyloxycarbonyl, 1-methylcyclopentanyloxycarbonyl, cyclohexanyloxy-carbonyl, 1-methylcyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-toluylsulfonyl)ethoxycarbonyl, 2-(methylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphino)-ethoxycarbonyl, 9-fluorenylmethoxycarbonyl ("Fmoc"), 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, isobornyloxycarbonyl, 1-piperidyloxycarbonyl, benzyloxycarbonyl ("Cbz"), 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxy-carbonyl, α-2,4,5,-tetramethylbenzyloxycarbonyl ("Tmz"), 4-methoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-cyanobenzyloxycarbonyl, 4-(decyloxy)benzyloxycarbonyl and the like; the benzoylmethylsulfonyl group, dithiasuccinoyl ("Dts"), the 2-(nitro)phenylsulfenyl group ("Nps"), the diphenyl-phosphine oxide group and like amino-protecting groups. The species of amino-protecting group employed is not critical so long as the derivatized amino group is stable to the conditions of the subsequent reaction(S) and can be removed at the appropriate point without disrupting the remainder of the compounds. Preferred amino-protecting groups are Boc, Cbz and Fmoc. Further

examples of amino-protecting groups embraced by the above term are well known in organic synthesis and the peptide art and are described by, for example, T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis," 2nd ed., John Wiley and Sons, New York, NY, 1991, Chapter 7, M. Bodanzsky, "Principles of Peptide Synthesis," 1st and 2nd revised ed., Springer-Verlag, New York, NY, 1984 and 1993, and Stewart and Young, "Solid Phase Peptide Synthesis," 2nd ed., Pierce Chemical Co., Rockford, IL, 1984, each of which is incorporated herein by reference. The related term "protected amino" defines an amino group substituted with an amino-protecting group discussed above. In addition, the term "protected carboxamide" means there is an amino-protecting group on the carboxamide nitrogen.

The term "carboxy-protecting group" as used herein refers to one of the ester derivatives of the carboxylic acid group commonly employed to block or protect the carboxylic acid group while reactions are carried out on other functional groups on the compound. Examples of such carboxylic acid protecting groups include t-butyl, 4-nitrobenzyl, 4-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, pentamethylbenzyl, 3,4-methylenedioxybenzyl, benzhydryl, 4,4'-dimethoxytrityl, 4,4',4"-trimethoxytrityl, 2-phenylpropyl, trimethylsilyl, t-butyldimethylsilyl, phenacyl, 2,2,2-trichloroethyl, β-(trimethylsilyl)ethyl, β-(di(n-butyl)methylsilyl)ethyl, *p*-toluenesulfonylethyl, 4-nitrobenzylsulfonylethyl, allyl, cinnamyl, 1-(trimethylsilylmethyl)-propenyl and like moieties. The species of carboxy-protecting group employed is not critical so long as the derivatized carboxylic acid is stable to the conditions of subsequent reaction(S) and can be removed at the appropriate point without disrupting the remainder of the molecule. Further

examples of these groups are found in E. Haslam, "Protective Groups in Organic Chemistry," J.G.W. McOmie, Ed., Plenum Press, New York, NY, 1973, Chapter 5, and T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis," 2nd ed., John Wiley and Sons, New York, NY, 1991, Chapter 5, each of which is incorporated herein by reference. A related term is "protected carboxy," which refers to a carboxy group substituted with one of the above carboxy-protecting groups.

The term "hydroxy-protecting group" refers to readily cleavable groups bonded to hydroxyl groups, with the hydroxy becoming a "protected hydroxy". In addition, the term "protected hydroxymethyl" means there is a readily cleavable groups bonded to hydroxyl portion of the hydroxymethyl group. Examples of such readily cleavable groups bonded to hydroxyl groups include the tetrahydropyranyl, 2-methoxypropyl, 1-ethoxyethyl, methoxymethyl, 2-methoxyethoxymethyl, methylthiomethyl, t-butyl, t-amyl, trityl, 4-methoxytrityl, 4,4'-dimethoxytrityl, 4,4',4"-trimethoxytrityl, benzyl, allyl, trimethylsilyl, (t-butyl)dimethylsilyl, 2,2,2-trichloroethoxycarbonyl groups and the like. The species of hydroxy-protecting groups is not critical so long as the derivatized hydroxyl group is stable to the conditions of subsequent reaction(S) and can be removed at the appropriate point without disrupting the remainder of the molecule. Further examples of hydroxy-protecting groups are described by C.B. Reese and E. Haslam, "Protective Groups in Organic Chemistry," J.G.W. McOmie, Ed., Plenum Press, New York, NY, 1973, Chapters 3 and 4, respectively, and T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis," 2nd ed., John Wiley and Sons, New York, NY, 1991, Chapters 2 and 3.

The term "C_1 to C_4 alkylthio" refers to sulfide groups such as methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, t-butylthio and like groups.

The term "C_1 to C_4 alkylsulfoxide" indicates sulfoxide groups such as methylsulfoxide, ethylsulfoxide, n-propylsulfoxide, isopropylsulfoxide, n-butylsulfoxide, sec-butylsulfoxide and the like.

The term "C_1 to C_4 alkylsulfonyl" encompasses groups such as methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, t-butylsulfonyl and the like.

By "substituted phenylthio," "substituted phenyl sulfoxide," and "substituted phenylsulfonyl" is meant that the phenyl can be substituted as described above in relation to "substituted phenyl."

The terms "cyclic C_2 to C_7 alkylene," "substituted cyclic C_2 to C_7 alkylene," "cyclic C_2 to C_7 heteroalkylene," and "substituted cyclic C_2 to C_7 heteroalkylene," define such a cyclic group bonded ("fused") to the phenyl radical resulting in a bicyclic ring system. The cyclic group may be saturated or contain one or two double bonds. Furthermore, the cyclic group may have one or two methylene or methine groups replaced by one or two oxygen, nitrogen or sulfur atoms which are the the cyclic C_2 to C_7 heteroalkylene.

The cyclic alkylene or heteroalkylene group may be substituted once or twice by the same or different substituents selected from the group consisting of the following moieties: hydroxy, protected hydroxy, carboxy, protected carboxy, oxo, protected oxo, C_1 to C_4 acyloxy, formyl, C_1 to C_7 acyl , C_1 to C_6 alkyl, carbamoyl, C_1 to C_7 alkoxy, C_1 to C_4 alkylthio, C_1 to C_4 alkylsulfoxide, C_1 to

C_4 alkylsulfonyl, halo, amino, protected amino, (monosubstituted)amino, protected (monosubstitued)amino, (disubstituted)amino, hydroxymethyl or a protected hydroxymethyl.

The cyclic alkylene or heteroalkylene group fused onto the benzene radical can contain two to ten ring members, but it preferably contains three to six members. Examples of such saturated cyclic groups are when the resultant bicyclic ring system is 2,3-dihydro-indanyl and a tetralin ring. When the cyclic groups are unsaturated, examples occur when the resultant bicyclic ring system is a naphthyl ring or indolyl. Examples of fused cyclic groups which each contain one nitrogen atom and one or more double bond, preferably one or two double bonds, are when the phenyl is fused to a pyridino, pyrano, pyrrolo, pyridinyl, dihydropyrrolo, or dihydropyridinyl ring. Examples of fused cyclic groups which each contain one oxygen atom and one or two double bonds are when the phenyl ring is fused to a furo, pyrano, dihydrofurano, or dihydropyrano ring. Examples of fused cyclic groups which each have one sulfur atom and contain one or two double bonds are when the phenyl is fused to a thieno, thiopyrano, dihydrothieno or dihydrothiopyrano ring. Examples of cyclic groups which contain two heteroatoms selected from sulfur and nitrogen and one or two double bonds are when the phenyl ring is fused to a thiazolo, isothiazolo, dihydrothiazolo or dihydroisothiazolo ring. Examples of cyclic groups which contain two heteroatoms selected from oxygen and nitrogen and one or two double bonds are when the benzene ring is fused to an oxazolo, isoxazolo, dihydrooxazolo or dihydroisoxazolo ring. Examples of cyclic groups which contain two nitrogen heteroatoms and one or two double bonds occur when the benzene ring is fused to a pyrazolo, imidazolo, dihydropyrazolo or dihydroimidazolo ring or pyrazinyl.

The term "amino acid" includes any one of the twenty naturally-occurring amino acids or the D-form of any one of the naturally-occurring amino acids. In addition, the term "amino acid" also includes other non-naturally occurring amino acids besides the D-amino acids, which are functional equivalents of the naturally-occurring amino acids. Such non-naturally-occurring amino acids include, for example, norleucine ("Nle"), norvaline ("Nva"), β-Alanine, L- or D-naphthalanine, ornithine ("Orn"), homoarginine (homoArg) and others well known in the peptide art, such as those described in M. Bodanzsky, "Principles of Peptide Synthesis," 1st and 2nd revised ed., Springer-Verlag, New York, NY, 1984 and 1993, and Stewart and Young, "Solid Phase Peptide Synthesis," 2nd ed., Pierce Chemical Co., Rockford, IL, 1984, both of which are incorporated herein by reference. Amino acids and amino acid analogs can be purchased commercially (Sigma Chemical Co.; Advanced Chemtech) or synthesized using methods known in the art.

The amino acids are indicated herein by either their full name or by the commonly known three letter code. Further, in the naming of amino acids, "D-" designates an amino acid having the "D" configuration, as opposed to the naturally occurring L-amino acids. Where no specific configuration is indicated, one skilled in the art would understand the amino acid to be an L-amino acid. The amino acids can, however, also be in racemic mixtures of the D- and L-configuration.

As used herein, the phrase "any one of the twenty naturally-occurring amino acids" means any one of the following: Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val. As used herein, the language "the D-form of a naturally-occurring amino acid" means the D-isomer of any

one of these naturally-occurring amino acids, with the exception of Gly, which does not occur as D or L isomers.

One or more of the isoquinoline derivatives, even within a given library, may be present as a salt. The term "salt" encompasses those salts that form with the carboxylate anions and amine nitrogens and include salts formed with the organic and inorganic anions and cations discussed below. Furthermore, the term includes salts that form by standard acid-base reactions with basic groups (such as amino groups) and organic or inorganic acids. Such acids include hydrochloric, sulfuric, phosphoric, acetic, succinic, citric lactic, maleic, fumaric, palmitic, cholic, pamoic, mucic, D-glutamic, d-camphoric, glutaric, phthalic, tartaric, lauric, stearic, salicyclic, methanesulfonic, benzenesulfonic, sorbic, picric, benzoic, cinnamic, and like acids.

The term "organic or inorganic cation" refers to counterions for the carboxylate anion of a carboxylate salt. The counter-ions are chosen from the alkali and alkaline earth metals, (such as lithium, sodium, potassium, barium, aluminum and calcium); ammonium and mono-, di- and tri-alkyl amines such as trimethylamine, cyclohexylamine; and the organic cations, such as dibenzylammonium, benzylammonium, 2-hydroxyethylammonium, bis(2-hydroxyethyl)ammonium, phenylethylbenzylammonium, dibenzylethylenediammonium, and like cations. See, for example, "Pharmaceutical Salts," Berge et al., J. Pharm. Sci., 66:1-19 (1977), which is incorporated herein by reference. Other cations encompassed by the above term include the protonated form of procaine, quinine and N-methylglucosamine, and the protonated forms of basic amino acids such as glycine, ornithine, histidine, phenylglycine, lysine and arginine. Furthermore, any

zwitterionic form of the instant compounds formed by a carboxylic acid and an amino group is referred to by this term. For example, a cation for a carboxylate anion will exist when R_2 or R_3 is substituted with a (quaternary ammonium)methyl group. A preferred cation for the carboxylate anion is the sodium cation.

The compounds of the above formula can also exist as solvates and hydrates. Thus, these compounds may crystallize with, for example, waters of hydration, or one, a number of, or any fraction thereof of molecules of the mother liquor solvent. The solvates and hydrates of such compounds are included within the scope of this invention.

One or more isoquinoline derivatives, even when in a library, can be in the biologically active ester form, such as the non-toxic, metabolically-labile ester-form. Such ester forms induce increased blood levels and prolong the efficacy of the corresponding non-esterified forms of the compounds. Ester groups which can be used include the lower alkoxymethyl groups, for example, methoxymethyl, ethoxymethyl, isopropoxymethyl and the like; the α-(C_1 to C_7) alkoxyethyl groups, for example methoxyethyl, ethoxyethyl, propoxyethyl, isopropoxyethyl and the like; the 2-oxo-1,3-diooxlen-4-ylmethyl groups, such as 5-methyl-2-oxo-1,3-dioxolen-4-ylmethyl, 5-phenyl-2-oxo-1,3-dioxolen-4-ylmethyl and the like; the C_1 to C_4 alkylthiomethyl groups, for example methylthiomethyl, ethylthiomethyl, iso-propylthiomethyl and the like; the acyloxymethyl groups, for example pivaloyloxymethyl, pivaloyloxyethyl, α-acetoxymethyl and the like; the ethoxycarbonyl-1-methyl group; the α-acetoxyethyl; the 1-(C_1 to C_7 alkyloxycarbonyloxy)ethyl groups such as the 1-(ethoxycarbonyloxy)ethyl group; and the 1-(C_1 to C_7 alkylaminocarbonyloxy)ethyl groups such as the 1-(methylaminocarbonyloxy)ethyl group.

The term "array" is used merely to catagorize or group a collection of individually synthesized compounds based on certain commonality of one or more R substituents. Although compounds individually synthesized and screened as in ensuing examples, libraries containing such compounds can also be prepared by the synthetic scheme of the examples below using well known combinatorial chemistry. Therefore, libraries containing isoquinoline compounds as disclosed herein are included within the invention.

The library prepared from the above mentioned method can be useful for screening the library on the resin or alternatively can be cleaved from the resin as discrete compounds and screened in absence of resin. Preferably, the methods described above further comprise the step of cleaving the library from the resin to give discrete compounds.

As used herein, a chemical or combinatorial "library" is an intentionally created collection of differing molecules which can be prepared by the synthetic means provided below or otherwise and screened for biological activity in a variety of formats (e.g., libraries of soluble molecules, libraries of compounds attached to resin beads, silica chips or other solid supports). The libraries can be screened in any variety of melanocortin receptor and related activity assays, such as those detailed below as well as others known in the art. The libraries will generally have at least one active compound and are generally prepared in such that the compounds are in equimolar quantities.

Compounds disclosed in previous work that are not in an intentially created collection are not part of

a "combinatorial library" of the invention. In addition, compounds that are in an unintentional or undesired

mixture are not part of a "combinatorial library" of the invention.

"Combinatorial chemistry" or "combinatorial synthesis" refers to the parallel synthesis of diverse compounds by sequential addition of reagents which leads to the generation of large chemical libraries having molecular diversity. Combinatorial chemistry, therefore, involves the systematic and repetitive, covalent connection of a set of different "building blocks" of varying structures to yield large arrays of diverse molecular entities.

A combinatorial library of the invention can contain two or more of the above-described compounds. The invention further provides a combinatorial library containing five or more of the above-described compounds. In another embodiment of the invention, a combinatorial library can contain ten or more of the above-described compounds. In yet another embodiment of the invention, a combinatorial library can contain fifty or more of the above-described compounds. If desired, a combinatorial library of the invention can contain 100,000 or more, or even 1,000,000 or more, of the above-described compounds.

By way of example, the preparation of the combinatorial libraries can use the "split resin approach." The split resin approach is described by, for example, U.S. Patent 5,010,175 to Rutter, WO PCT 91/19735 to Simon, and Gallop et al., *J. Med. Chem.*, 37:1233-1251 (1994), all of which are incorporated herein by reference.

In addition to the above isoquinoline compounds, which are MC receptor ligands, other isoquinoline compounds can also function as MC receptor

ligands. Other isoquinoline compounds that can function as MC receptor ligands include the isoquinoline derivatives and isoquinoline compound libraries described in Kiely et al., "Isoquinoline Derivatives and Isoquinoline Combinatorial Libraries," U.S. Patent Application Serial No. 08/734,516, filed October 18, 1996, which is incorporated herein by reference.

MC receptor ligands such as the isoquinoline compounds disclosed herein can be synthesized using the methods of synthesis described in Example I below. The choice of chemical functional groups incorporated into specific positions on isoquinoline compounds will depend, in part, on the specific physical, chemical or biological characteristics required of the MC receptor ligand. Such characteristics are determined, in part, by the route by which the MC receptor ligand will be administered or the location in a subject to which the MC receptor ligand will be directed.

As used herein, the term "ligand" means a molecule that can selectively bind to a receptor. For example, a MC receptor ligand can selectively bind to a MC receptor. Those skilled in the art know what is meant by the term ligand. The isoquinoline compounds described herein are MC receptor ligands. A ligand can function as an agonist or antagonist. As used herein, the term "agonist" means that a ligand has the function of mimicking the physiological activity of another molecule. For example, a MC receptor ligand that functions as an agonist mimics the physiological activity of a MC receptor ligand such as MSH, which stimulates MC receptor activity. Similarly, the term "antagonist" means that a ligand has the function of reducing the physiological activity of another molecule, for example, by preventing the activation or inhibiting the activity of a receptor.

For example, a MC receptor ligand that functions as an antagonist reduces the physiological activity of a MC receptor. A reduction in MC receptor activity can be due to the antagonist binding to the MC receptor and inhibiting activation or to the antagonist preventing the binding of a ligand that stimulates MC receptor activity.

The invention provides methods for altering the activity of a MC receptor in a subject by administering to the subject an effective amount of a MC receptor ligand, wherein the MC receptor ligand comprises an isoquinoline compound. The MC receptor ligands can be the isoquinoline compounds having the structures described above.

Many of the physiological effects of known MC receptor ligands on MC receptor activity are mediated by cytokines, and MC receptor ligands alter cytokine activity. Due to the effect of MC receptor signaling on cytokines, the MC receptor ligands of the invention can function as cytokine regulatory agents by regulating the aberrant or altered expression of one or more cytokines that occurs in various conditions, including, for example, pathologies, immune responses and inflammatory responses. Such conditions are considered together for purposes of the present invention in that they are characterized, in part, by altered or aberrant cytokine activity and, therefore, are amenable to regulation by one or more cytokine regulatory agents such as the MC receptor ligands disclosed herein.

It should be recognized, however, that while the MC receptor ligands of the invention can function as cytokine regulatory agents, no specific mechanism of action is proposed as to how a MC receptor ligand acts to affect a condition. The MC receptor ligands of the

invention can be used to treat conditions characterized by altered or aberrant cytokine activity. However, the conditions treatable with the MC receptor ligands of the invention are not restricted to those conditions or diseases involving altered cytokine activity. The MC receptor ligands are useful for treating a disease or condition if the MC receptor ligand prevents the disease or improves signs or symptoms of the disease, regardless of the mechanism causing the signs or symptoms of the disease.

The effects of isoquinoline compounds, which bind to MC receptors and have the structures described above, on cytokines are similar to those for cytokine regulatory agents such as HP 228, which has the amino acid sequence Ac-Nle-Gln-His-(D)Phe-Arg-(D)Trp-Gly-NH_2 (see Examples VI to IX). The amino acids are designated by their well known three letter codes, with the amino acids in the L- configuration except those specifically indicated as the D- configuration. Nle represents norleucine. The amino-terminus is acetylated and the carboxyl-terminus is amidated. The effect of HP 228 on cytokines and the uses provided thereby are described, for example, in U.S. Patent No. 5,420,109, WO 95/13086 and WO 96/27386, each of which is incorporated herein by reference. The present invention provides a method of restraining a pathologically elevated cytokine activity in a subject by administering to the subject an effective amount of MC receptor ligands such as isoquinoline compounds. The pathologically elevated cytokine activity can be due, for example, to inflammation, cachexia, or a patho-immunogenic disease.

Aberrant cytokine expression can result in damage to healthy tissue in a subject and, in extreme cases, can lead to severe disability and death.

Cytokines can be expressed at a site of localized infection or can be expressed systemically, for example, in an immune response or in response to bacterial endotoxin-induced sepsis. Cytokine expression can induce pyrexia (fever) and hyperalgesia (extreme sensitivity to pain) in a subject, as well as macrophage and monocyte activation, which produces or further contributes to an inflammatory response in a subject.

As used herein, the terms "regulate" or "regulatory" mean to control by enhancing, limiting, restricting, restraining, modulating or moderating. Such regulation includes the pleiotropic, redundant, synergistic or antagonistic effects that occur due to the activity of biological agents such as cytokines, which can affect a variety of biological functions directly or indirectly through cascade or biofeedback mechanisms.

As used herein, the term "cytokine regulatory agent" means an agent that controls cytokine activity by enhancing, limiting, restricting, restraining, modulating or moderating the biological activity of a cytokine. It should be recognized, however, that while the cytokine regulating agents generally can regulate cytokine activity, no specific mechanism of action is proposed as to how a cytokine regulatory agent acts to affect a condition characterized by altered or aberrant cytokine activity.

Cytokines are well known in the art and include, but are not limited to the tumor necrosis factors (TNFs), colony stimulating factors (CSFs), interferons (INFs), interleukins (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, and IL-15), transforming growth factors (TGFs), oncostatin M (OSM), leukemia inhibiting factor (LIF),

platelet activating factor (PAF) and other soluble immunoregulatory peptides that mediate host defense responses, cell regulation and cell differentiation (see, for example, Kuby, Immunology 3rd ed. (W.H. Freeman and Co., New York (1997); see Chapter 13, which is incorporated herein by reference).

As used herein, the term "characterized by" means contributes or affects, at least in part. Though cytokine contribution can be, it does not have to be, the only, primary, or even a major factor of the condition. For example, it is well understood in the art that an infection has altered cytokine levels and is, therefore, a condition characterized by cytokine activity, although cytokine activity is only a part of the infectious condition.

As used herein, the term "condition characterized by altered or aberrant cytokine activity" includes all cytokine regulated or modulated pathologies and injuries, including the immune, inflammatory and healing processes associated with an injury or disease. The skilled artisan can recognize such a condition by detecting an increased or decreased level or activity of a particular cytokine as compared to the normal level of the cytokine expected to be found in a healthy individual. Methods for determining such normal levels are well known in the art and can be determined by sampling a statistically significant number of subjects in the population.

As used herein, the term "pathologically elevated" means that a cytokine activity is elevated above a range of activities which is expected in a normal population of such subjects and which is associated with a pathological response. For example, a normal range of

interleukin activity, such as IL-1β activity, present in a specific tissue can be determined by sampling a number of subjects in the population. A subject having a pathology characterized by cytokine-induced pathological effects can be readily identified by determining that the cytokine activity in the subject is pathologically elevated above the normal range. In particular, a pathologically elevated level of cytokine activity is at least about one standard deviation above the normal, and can be at least two standard deviations above the normal range.

A MC receptor ligand of the invention, such as an isoquinoline compound, can function as a cytokine regulatory agent and can be used to decrease the activity of a cytokine. For example, a particular pathological condition can cause an increase in the level or activity of a cytokine. A MC receptor ligand that functions to restrain cytokine activity can be used to reduce the level or activity of the elevated cytokine. Such a reduction in cytokine activity can alleviate the symptoms of the pathological condition. As disclosed herein, isoquinoline compounds of the invention can effectively decrease the level of TNF-α (see Example VI and Table 4). Isoquinoline compounds that are particularly effective at decreasing TNF-α include TRG 2405-190, TRG 2405-241, TRG 2405-252, TRG 2405-253 and TRG 2408-30.

A MC receptor ligand of the present invention can function as a cytokine regulatory agent, or composition containing the agent, and can be used to increase the physiologic level of one or more cytokines. For example, a particular condition can decrease the level or activity of a cytokine, which can inhibit all or part of an immune response or the immune system. Administration of a cytokine regulatory agent in a

pharmacologically efficacious dose can enhance the level or activity of the cytokine, thereby reducing the level of immunosuppression.

A MC receptor ligand such as the isoquinoline compounds disclosed herein can function as a cytokine regulatory agent and increase the levels of IL-10 in a mammal such as a human. IL-10 can block the activation of some inflammatory cytokines, including TNF, IL-1 and IL-6, while up-regulating cytokines such as IL-12. IL-10 also stimulates the proliferation of mast cells and thymocytes. IL-10 inhibits several monocyte and macrophage functions, including, for example, antigen presentation to T cells by depressing Class II MHC expression; synthesis of IL-1, IL-6, IL-8, CSF, and TNF; and microbicidal activities. The inhibited microbicidal activities include suppressing production of nitrogen oxides and bactericidal metabolites. As a consequence of monocyte and macrophage IL-10 mediated inhibition, activity of some types of helper T cells is inhibited. Particularly, the T_H1 cells, which are responsible for cell-mediated functions such as delayed-type hypersensitivity cells, and cytotoxic T cells are inhibited. As a further consequence of T_H1 cell inhibition, activity of the T_H2 cells is augmented, particularly the T cell subset that augments B cell activation, bacterial and helminthic resistance and allergic reactions.

As disclosed herein, administration of a MC receptor ligand can increase the plasma levels of IL-10 in mammals (see Example VII and Table 4) and, therefore, can be useful for modulating, for example, immunoresponsiveness in a subject. Isoquinoline compounds that are particularly effective at increasing

IL-10 include TRG 2405-190, TRG 2405-241, TRG 2405-252, TRG 2405-253 and TRG 2408-30.

The binding of a MC receptor ligand to a MC receptor results in a wide range of physiological responses. MC receptors are G protein-coupled receptors that activate adenylate cylcase and produce cAMP in response to binding of ligands such as MSH. Although many of the physiological effects of MC receptor signaling are mediated by cytokines, MC receptor ligands of the invention are not limited to those that regulate cytokine activity, as discussed above, but can be any MC receptor ligand that functions to alleviate the signs or symptoms of a disease or condition. Therefore, MC receptor ligands are useful for exploiting the various physiological responses mediated by MC receptor signaling.

The diversity of physiological responses to MC receptor signaling can be advantageously used to alter or regulate a physiological pathway that mediates or moderates a pathological condition or disease. The recent elucidation of the role of specific MC receptors in particular physiological pathways supports the use of ligands that activate specific MC receptors to modulate a physiological effect that results in a a given condition or disease. Therefore, MC receptor ligands of the invention, which alter the activity of a MC receptor that mediates or moderates a given condition or disease, are useful for treating that condition or disease.

MCR-1 is involved in pain and inflammation and, therefore, MC receptor ligands that alter the activity of MCR-1 are particularly useful for treating pain and inflammation. In one embodiment, a MC receptor ligand such as an isoquinoline compound can be used as an

analgesic or anti-inflammatory agent. α-MSH has been shown to inhibit migration and chemotaxis of neutrophils, which express MCR-1 (Catania et al., *supra*). The inhibition by α-MSH was associated with changes in neutrophil cyclic AMP (cAMP) levels. MC receptors are G-protein coupled receptors that couple to adenylate cyclase and produce cAMP upon activation. The inhibition of neutrophil chemotaxis is associated with the anti-inflammatory activity of α-MSH. Since α-MSH has anti-inflammatory activity, the MC receptor ligands of the invention, such as isoquinoline compounds, can similarly function as anti-inflammatory agents, for example, by reducing neutrophil chemotaxis.

MC receptor ligands such as isoquinoline compounds are useful for reducing inflammation. As described in Example VIII, administration of TRG 2405-190, TRG 2405-241, TRG 2405-252, TRG 2405-253, TRG 2409-2 and TRG 2409-14 reduced inflammation in response to arachadonic acid administration. These results show that MC receptor ligands such as isoquinoline compounds, and particularly TRG 2405-190, TRG 2405-241, TRG 2405-252, TRG 2405-253, TRG 2409-2 and TRG 2409-14, are useful for reducing inflammation.

Nitric oxide (NO) is induced during inflammation by a variety of proinflammatory cytokines. α-MSH was shown to inhibit production of NO through reduction of NO synthase and NO synthase mRNA (Star et al., Proc. Natl. Acad. Sci. USA 92:8016-8020 (1995)). Similarly, MC receptor ligands of the invention, such as isoquinoline compounds, can be used to inhibit NO production, thereby reducing inflammation.

MC receptor ligands that activate MCR-4 are particularly useful for decreasing body weight. MCR-4

has been shown to function in regulating food intake and weight gain. Targeted disruption of MCR-4 causes mice to develop a maturity onset obesity associated with hyperphagia, hyperinsulinemia and hyperglycemia (Huszar et al., *supra*). Further evidence for the role of MC receptors in regulating food intake and weight gain involves the function of the agouti protein, which is a MCR-4 antagonist. An agouti-related protein functions as a selective antagonist of MCR-3 and MCR-4 and causes obesity in transgenic mice expressing agouti-related protein (Ollman et al., Science 278:135-137 (1997)). Furthermore, agouti analogs were injected into the brains of mice, and those analogs that functioned as MC receptor agonists inhibited feeding while those agouti analogs that functioned as antagonists increased feeding (Fan et al. *supra*). Thus, a functional role for MC receptors in regulating food intake and weight gain has been established. Therefore, the MC receptor ligands of the invention such as isoquinoline compounds are useful for treating obesity by decreasing food intake and body weight gain.

As disclosed herein, administration of an isoquinoline compound to rats resulted in a significant decrease in the rate of body weight gain and a significant decrease in body weight (see Example IX). As used herein, the term "decrease in body weight" is used broadly to mean an actual decrease in body weight or a decrease in the rate of body weight gain over time, as compared to the normal weight gain expected in the period of time. The isoquinoline compounds TRG 2405-190, TRG 2405-241, TRG 2405-252 and TRG 2405-253 are particularly effective at reducing body weight and food consumption. These results indicate that a MC receptor ligand can cause a decrease in the rate of body weight gain and a decrease in food consumption.

An association between MC receptor signaling and body energy and metabolism has been reported (Huszar et al., *supra*). The MC receptor ligand HP 228 has been shown to modulate acute resting oxygen consumption (Omholt et al., The Pharmacologist, 39:53 (1997)), which is incorporated herein by reference. Therefore, MC receptor ligands of the invention can also be used for modulating the metabolic rate or acute oxygen consumption in a subject. The modulated metabolic rate can lead to a decrease in body weight. Thus, MC receptor ligands that can modulate the metabolic rate or acute oxygen consumption in a subject are particularly useful for decreasing body weight in a subject. The MC receptor ligands of the invention can be used to treat obesity and can independently or in combination affect body weight by decreasing food consumption or modulating metabolic rate or oxygen consumption.

In addition to MC receptor ligands that function as agonists that stimulate MC receptor activity, the invention also provides MC receptor ligands, such as isoquinoline compounds, that function as antagonists that inhibit MC receptor activity. MC receptor antagonists can be used, for example, to increase food intake and body weight analogous to that observed with the MC receptor antagonist agouti protein and the agouti analogs that function as antagonists (Fan et al., *supra*). MC receptor ligands that function as antagonists are particularly useful for increasing food intake and body weight in an individual suffering from cachexia, a general weight loss that occurs during chronic disease or emotional disturbance.

MC receptor ligands of the invention can also function as cytokine regulatory agents that are useful for treating diabetes. A link exists between obesity and

non-insulin dependent diabetes mellitus (NIDDM) (Hotamisligil and Spiegelman, Diabetes 43:1271-1278 (1994a)). Therefore, MC receptor ligands are useful for decreasing the weight of an obese subject to prevent or alleviate the symptoms associated with NIDDM. Increased TNF-α expression has been detected in the adipose tissue of obese individuals and has been suggested to have a role in the appearance of NIDDM in these individuals (Hotamisligil et al., J. Clin. Invest. 95:2409-2415 (1995)). However, efforts to neutralize TNF activity using an antibody that binds the TNF receptor did not result in significant weight loss when examined in a rat obesity/diabetes model, the Zucker fa/fa rat model (Hotamisligil et al., J. Clin Invest. 94:1543-1549 (1994b)). Therefore, MC receptor ligands of the invention that decrease TNF-α are particularly useful for treating diabetes and associated obesity.

The α-MSH analog MELANOTAN-II has been shown to cause penile erections in human subjects in pilot phase I clinical studies (Dorr et al., Life Sciences 58:1777-1784 (1996)). Therefore, MC receptors ligands of the invention can be used to treat erectile dysfunction in a subject (see Example X and Figures 8 and 9). Further examples of compounds include any of the isoquinolines described herein, including those in TRG 2411.

Other conditions that can be treated with the MC receptor ligands of the invention such as isoquinoline compounds include, but are not limited to, disuse deconditioning; organ damage such as occurs in response to organ transplantation or ischemic injury such as that which can occur after reperfusion or stroke; adverse reactions associated with cancer chemotherapy; diseases such as atherosclerosis that are mediated by free

radicals and nitric oxide action; bacterial endotoxic sepsis and related shock; adult respiratory distress syndrome; and autoimmune or other patho-immunogenic diseases or reactions such as allergic reactions or anaphylaxis, rheumatoid arthritis, inflammatory bowel disease, ulcerative colitis, glomerulonephritis, systemic lupus erythematosus, transplant atherosclerosis and parasitic mediated immune dysfunctions such as Chagas' Disease. Many of these conditions are characterized by altered or aberrant cytokine activity.

A variety of assays can be used to identify or characterize MC receptor ligands of the invention. For example, the ability of an isoquinoline compound to compete for binding of a known MC receptor ligand can be used to assess the affinity and specificity of an isoquinoline compound for one or more MC receptors. Any MC receptor ligand can be used so long as the ligand can be labeled with a detectable moiety. The detectable moiety can be, for example, a radiolabel, fluorescent label or chromophore, or any detectable functional moiety so long as the MC receptor ligand exhibits specific MC receptor binding. As described in Example II, a particularly useful detectable MC receptor ligand for identifying and characterizing other MC receptor ligands is ^{125}I-HP 467, which has the amino acid sequence Ac-Nle-Gln-His-(*p*(I)-D-Phe)-Arg-(D-Trp)-Gly-NH_2 and is described in Dooley et al., "Melanocortin Receptor Ligands and Methods of Using Same," U.S. patent application 09/027,108, filed February 20, 1998, which is incorporated herein by reference. HP 467 is a *para*-iodinated form of HP 228. The results described in Example IV below indicate that a number of MC receptor ligands can be identified using a detectable MC receptor ligand.

Using assay methods such as those described above and in Example II, binding kinetics and competition with radiolabeled HP 467 confirmed that isoquinoline compounds of the invention bind to one or more MC receptors (see Examples II and IV). Furthermore, the assays revealed that isoquinoline compounds of the invention exhibited a range of affinities and specificity for various MC receptors.

A variety of isoquinoline compounds that bind to MCR-1 and MCR-4 and are MC receptor ligands are shown in Table 1. Isoquinoline compounds that are particularly effective MC receptor ligands include TRG 2405-190, TRG 2405-239, TRG 2405-241, TRG 2405-252, TRG 2405-253, TRG 2408-30, TRG 2408-57, TRG 2408-62, TRG 2409-2, TRG 2409-14, TRG 2411-26, TRG 2411-50, TRG 2411-60, TRG 2411-111 and TRG 2411-186.

Some of the isoquinoline compounds were further tested for binding activity to MCR-3 and MCR-5. The results of these MCR-3 and MCR-5 binding studies are shown in Table 2. Various isoquinoline compounds of the invention exhibit binding activity to one or more MC receptors.

The invention provides MC receptor ligands that bind to several MC receptors with similar affinity (see Tables 1 and 2). In addition, the invention also provides MC receptor ligands that show selectivity for one or more MC receptors. As used herein, the term "selectivity" means that the affinity of a MC receptor ligand differs between one MC receptor and another by about 10-fold, generally about 20- to 50-fold, and particularly about 100-fold. In some cases, a MC receptor ligand having broad specificity is desired. In other cases, it is desirable to use MC receptor ligands

having selectivity for a particular MC receptor. For example, MCR-1 ligands are particularly useful for treating pain and inflammation, whereas MCR-4 ligands are useful for treating obesity. The binding characteristics and specificity of a given MC receptor ligand can be selected based on the particular disease or physiological effect that is desired to be altered.

Another assay useful for identifying or characterizing MC receptor ligands measures signaling of MC receptors. MC receptors are G protein-coupled receptors that couple to adenylate cyclase and produce cAMP. Therefore, measuring cAMP production in a cell expressing a MC receptor and treated with a MC receptor ligand can be used to assess the function of the MC receptor ligand in activating a MC receptor. One method for measuring cAMP production in cells expressing a MC receptor ligand and treated with an isoquinoline compound of the invention is described in Example III. The results described in Example V show that isoquinoline compounds can activate MC receptors and stimulate cAMP production. A variety of isoquinoline compounds that activate MC receptors are shown in Table 3.

The invention also relates to pharmaceutical compositions comprising a MC receptor ligand such as an isoquinoline compound and a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are well known in the art and include aqueous solutions such as physiologically buffered saline or other solvents or vehicles such as glycols, glycerol, oils such as olive oil or injectable organic esters.

A pharmaceutically acceptable carrier can contain physiologically acceptable compounds that act, for example, to stabilize the MC receptor ligand or

increase the absorption of the agent. Such physiologically acceptable compounds include, for example, carbohydrates, such as glucose, sucrose or dextrans, antioxidants, such as ascorbic acid or glutathione, chelating agents, low molecular weight proteins or other stabilizers or excipients. One skilled in the art would know that the choice of a pharmaceutically acceptable carrier, including a physiologically acceptable compound, depends, for example, on the route of administration of the MC receptor ligand and on the particular physico-chemical characteristics of the specific MC receptor ligand.

The invention further relates to methods of administering a pharmaceutical composition comprising an MC receptor ligand such as an isoquinoline compound to a subject in order to restrain pathologically elevated cytokine activity in the subject, to treat inflammation or to treat obesity. For example, an isoquinoline compound can be administered to a subject as a treatment for inflammation, pain, obesity or cachexia.

The invention also relates to methods of administering a pharmaceutical composition comprising an MC receptor ligand such as an isoquinoline compound to a subject in order to enhance a cytokine activity that restrains pathologically elevated cytokine activity in a subject. For example, IL-10 is known to decrease the activity of certain pathologically elevated cytokines such as TNF-α, IL-1, IL-6 and IL-8 (Platzer et al., International Immunol. 7:517-523 (1995)). A normal range of IL-10 activity present in a specific tissue can be determined by sampling a statistically significant number of normal, healthy subjects in the population. An isoquinoline compound is administered to increase IL-10 activity above the normal range in order to restrain

pathologically elevated cytokine activity. In particular, IL-10 cytokine activity is increased at least about one standard deviation above the normal, and can be two standard deviations or greater above the normal range.

A pharmaceutical composition comprising an MC receptor ligand such as an isoquinoline compound can be administered to a subject having pathologically elevated cytokine activity by various routes including, for example, orally, intravaginally, rectally, or parenterally, such as intravenously, intramuscularly, subcutaneously, intraorbitally, intracapsularly, intraperitoneally, intracisternally or by passive or facilitated absorption through the skin using, for example, a skin patch or transdermal iontophoresis, respectively. Furthermore, the composition can be administered by injection, intubation or topically, the latter of which can be passive, for example, by direct application of an ointment or powder, or active, for example, using a nasal spray or inhalant. An MC receptor ligand also can be administered as a topical spray, in which case one component of the composition is an appropriate propellant. The pharmaceutical composition also can be incorporated, if desired, into liposomes, microspheres or other polymer matrices (Gregoriadis, Liposome Technology, Vols. I to III, 2nd ed., CRC Press, Boca Raton, FL (1993), which is incorporated herein by reference). Liposomes, for example, which consist of phospholipids or other lipids, are nontoxic, physiologically acceptable and metabolizable carriers that are relatively simple to make and administer.

Since cytokine expression can be localized or systemic, one skilled in the art would select a particular route and method of administration of an

isoquinoline compound based on the source and distribution of cytokines in a subject. For example, in a subject suffering from a systemic condition such as bacterial endotoxin-induced sepsis, a pharmaceutical composition comprising an isoquinoline compound can be administered intravenously, orally or by another method that distributes the compound systemically. However, in a subject suffering from a pathology caused by localized cytokine expression such as acute respiratory distress syndrome, an isoquinoline compound can be suspended or dissolved in the appropriate pharmaceutically acceptable carrier and administered directly into the lungs using a nasal spray or other inhalation device.

In order to restrain the biological activity of a cytokine, an isoquinoline compound must be administered in an effective dose, which is about 0.0001 to 100 mg/kg body weight. The total effective dose can be administered to a subject as a single dose, either as a bolus or by infusion over a relatively short period of time, or can be administered using a fractionated treatment protocol, in which the multiple doses are administered over a more prolonged period of time. One skilled in the art would know that the concentration of an isoquinoline compound required to obtain an effective dose in a subject depends on many factors including the age and general health of the subject as well as the route of administration and the number of treatments to be administered. In view of these factors, the skilled artisan would adjust the particular dose so as to obtain an effective dose for altering the activity of a MC receptor.

The following examples are intended to illustrate but not limit the invention.

EXAMPLE I

Synthesis of Isoquinoline Compounds

This example shows the synthesis of isoquinoline compounds.

Isoquinoline compounds were synthesized essentially as described previously in U.S. Patent Application Serial No. 08/734,516, which is incorporated herein by reference.

An example of the reaction scheme representative of the synthesis of isoquinoline compounds is shown in Figures 1A and 1B. Figures 1A and 1B show a reaction scheme for synthesis of tetrahydroisoquinoline aromatic amines.

Briefly, for solid-phase synthesis of discrete tetrahydroisoquinoline aromatic amines, the appropriate number of porous polypropylene teabags were prepared, each containing polystyrene methylbenzhydrylamine (MBHA) resin (974 mg, 0.750 milliequivalents). One teabag was placed in a 60 mL bottle and washed with 5% (v/v) N,N,-diisopropylethylamine/dichloromethane (3 x 30 mL) followed by dichloromethane (DCM, 5 x 30 mL). A solution of N-(t-butyloxycarbonyl)glycine (657 mg, 3.75 mmoles), N-hydroxybenzotriazole (HOBt) (507 mg, 3.75 mmoles), and N,N-diisopropylcarbodiimide (DIC) (0.705 mL, 4.5 mmoles) was prepared in dimethylformamide (DMF) (37.5 mL) and added to the resin packet. After shaking for 16 hours the teabag was washed with DMF (3 x 30 mL) and DCM (3 x 30 mL). The same coupling procedure was performed on the remaining teabags, each being reacted with a separate amino acid from the following (R^1) list:
(S)-2-N-(t-butyloxycarbonyl)-3-N-(9-fluorenylmethoxycarbonyl)-diaminopropanoic acid,

(S)-2-N-(t-butyloxycarbonyl)-4-N-(9-fluorenylmethoxycarbonyl)-diaminobutanoic acid,
(S)-2-N-(t-butyloxycarbonyl)-5-N-(9-fluorenylmethoxycarbonyl)-diaminopentanoic acid,
(S)-2-N-(t-butyloxycarbonyl)-6-N-(9-fluorenylmethoxycarbonyl)-diaminohexanoic acid.

The teabag containing N-(t-butyloxycarbonyl)glycine on resin was washed with DCM (2 x 50 mL), shaken twice in 55% (v/v) trifluoroacetic acid (TFA)/DCM (30 mL, 30 min) and then washed with DCM (30 mL), isopropyl alcohol (2 x 30 mL), DCM (2 x 30 mL), 5% (v/v) diisopropylethylamine (DIEA)/DCM (3 x 30 mL, 2 min each) and DCM (3 x 30 mL). The remaining teabag was placed in one bottle and washed with DCM (150 mL, 15 minutes) and then treated with 20% (v/v) piperidine/DMF (150 mL, 10 minutes then again for 20 minutes). The bag was then washed with DMF (4 x 150 mL) and DCM (4 x 150 mL) and allowed to dry at room temperature.

The teabag containing glycine on resin was placed in a 20 mL bottle and treated with a solution of benzaldehyde (0.508 mL, 5 mmoles) and anhydrous trimethylorthoformate (1.094 mL, 10 mmoles) in anhydrous DMF (9 mL). After shaking for 3 hours, the packet was washed with anhydrous DMF (3 x 8 mL). A solution of homophthalic anhydride (801 mg, 5 mmoles) and triethylamine (0.044 mL, 0.3 mmoles) was prepared in DMF (10 mL) and added to the teabag. After shaking at room temperature for 16 hours the packet was washed with DMF (6 x 30 mL) and DCM (4 x 30 mL) and dried at room temperature.

The remaining teabags of amino acid on resin were each reacted as above in separate reactions with the

following 94 aldehydes such that all combinations of 4-carboxy disubstituted dihydroisoquinolones were formed as indicated in the following (R2) list:

2-hydroxybenzaldehyde (salicylaldehyde), 1,4-benzodioxan-6-carboxaldehyde, 1-methyl-2-pyrrolecarboxaldehyde, 1-naphthaldehyde, 2,3,4-trifluorobenzaldehyde, 2,3,5-trichlorobenzaldehyde, 2,3-(methylenedioxy)benzaldehyde, 2,3-difluorobenzaldehyde, 2,4-dichlorobenzaldehyde, 2,6-difluorobenzaldehyde, 2-bromobenzaldehyde, 2-chloro-5-nitrobenzaldehyde, 2-chloro-6-fluorobenzaldehyde, 2-cyanobenzaldehyde, 2-fluorobenzaldehyde, 2-furaldehyde, 2-imidazolecarboxaldehyde, 2-methoxybenzaldehyde (o-anisaldehyde), 2-naphthaldehyde, 2-pyridinecarboxaldehyde, 2-quinolinecarboxaldehyde, 2-thiophenecarboxaldehyde, 3,4-(methylenedioxy)benzaldehyde (piperonal), 3,4-dibenzyloxybenzaldehyde, 3,4-dichlorobenzaldehyde, 3,4-difluorobenzaldehyde, 3,5-bis(trifluoromethyl)benzaldehyde, 3,5-dibenzyloxybenzaldehyde, 3,5-dichlorobenzaldehyde, 3,5-dimethoxybenzaldehyde, 3,5-dimethyl-4-hydroxybenzaldehyde, 3-(3,4-dichlorophenoxy)benzaldehyde, 3-(4-methoxyphenoxy)benzaldehyde, 3-(trifluoromethyl)benzaldehyde, 3-bromo-4-fluorobenzaldehyde, 3-bromobenzaldehyde, 3-carboxybenzaldehyde, 3-cyanobenzaldehyde, 3-fluoro-4-methoxybenzaldehyde, 3-fluorobenzaldehyde, 3-furaldehyde, 3-hydroxybenzaldehyde, 3-methoxy-4-hydroxy-5-nitrobenzaldehyde, 3-methoxybenzaldehyde (m-anisaldehyde), 3-methyl-4-methoxybenzaldehyde, 3-methylbenzaldehyde (m-tolualdehyde), 3-nitro-4-chlorobenzaldehyde, 3-nitrobenzaldehyde, 3-phenoxybenzaldehyde,

3-pyridinecarboxaldehyde, 3-quinolinecarboxaldehyde, 3-thiophenecarboxaldehyde, 4-(3-dimethylaminopropoxy)benzaldehyde, 4-(dimethylamino)benzaldehyde, 4-(methylcarboxylate)benzaldehyde, 4-(methylthio)benzaldehyde, 4-(trifluoromethyl)benzaldehyde, 4-acetamidobenzaldehyde, 4-methoxybenzaldehyde (p-anisaldehyde), 4-biphenylcarboxaldehyde, 4-bromobenzaldehyde, 4-carboxybenzaldehyde, 4-cyanobenzaldehyde, 4-fluorobenzaldehyde, 4-hydroxybenzaldehyde, 4-isopropylbenzaldehyde, 4-methoxy-1-naphthaldehyde, 4-methylbenzaldehyde (p-tolualdehyde), 3-hydroxy-4-nitrobenzaldehyde, 4-nitrobenzaldehyde, 4-phenoxybenzaldehyde, 4-propoxybenzaldehyde, 4-pyridinecarboxaldehyde, 4-quinolinecarboxaldehyde, 5-(hydroxymethyl)-2-furaldehyde, 3-methoxy-4-hydroxy-5-bromobenzaldehyde, 5-methyl-2-thiophenecarboxaldehyde, 5-methyl-2-furaldehyde (5-methylfurfural), 5-nitro-2-furaldehyde, 6-methyl-2-pyridinecarboxaldehyde, 8-hydroxyquinoline-2-carboxaldehyde, 9-ethyl-3-carbazolecarboxaldehyde, 9-formyl-8-hydroxyjulolidine, pyrrole-2-carboxaldehyde, 3-hydroxy-4-methoxybenzaldehyde, 4-methylsulphonylbenzaldehyde, 4-methoxy-3-(sulfonic acid, Na)benzaldehyde, 5-bromo-2-furaldehyde, 2-thiazolecarboxaldehyde, 4-ethoxybenzaldehyde, 4-propoxybenzaldehyde, 4-butoxybenzaldehyde, 4-pentylaminobenzaldehyde, 4-amylbenzaldehyde.

The teabag containing glycine on resin (converted to the 4-carboxy disubstituted dihydroisoquinolone with benzaldehyde at R2) was placed in a 20 mL bottle. The teabag was treated with a solution of HOBt (410 mg, 3.0 mmoles), and DIC (0.56 mL,

3.6 mmoles) in anhydrous DMF (10 mL, 300 mM solution) and shaken for 20 minutes. The HOBt/DIC solution was decanted off of the teabags and anhydrous DMF (6.9 mL) and aniline (0.683 mL, 7.5 mmoles) was added. After shaking for 1 hour, the aniline solution was removed, and the bag was washed with anhydrous DMF (2 x 8 mL). The HOBt/DIC treatment was repeated followed by decanting and addition of a second aniline solution. This reaction was shaken at room temperature for 24 hours. The bag was then washed with DMF (3 x 8 mL), water (8 mL, 60 minutes), DMF (3 x 8 mL), DCM (3 x 8 mL), and allowed to dry.

The remaining teabags (containing 4-carboxy dihydroisoquinolones) were reacted as above in reactions with the following amines such that all combinations of trisubstituted dihydroisoquinolones were formed and denoted as a group as (X): N-methylaniline, 2-chloroaniline, 2-methoxyaniline, 3-chloroaniline, 3-ethoxyaniline, 3-aminophenol, 4-chloroaniline, 4-Methoxyaniline, benzylamine, N-benzylmethylamine, 2-chlorobenzylamine, 2-(trifluoromethyl)benzylamine, 2-methoxybenzylamine, 2-ethoxybenzylamine, 3-methoxybenzylamine, 3-(trifluoromethyl)benzylamine, 4-chlorobenzylamine, 4-methoxybenzylamine, 4-(trifluoromethyl)benzylamine, phenethylamine, 2-chlorophenethylamine, 2-methoxyphenethylamine, 3-chlorophenethylamine, 4-methoxyphenethylamine, 3-phenyl-1-propylamine, cyclopentylamine, isopropylamine, cycloheptylamine, N-methylcyclohexylamine, (aminomethyl)cyclohexane, piperidine, morpholine, 1-aminopiperidine, diethylamine, allylamine, isopropylamine, (2-aminoethyl)-trimethylammonium Cl-HCl, ammonia.

One teabag was left as the free carboxylic acid. Additional diversity at the R2 site was obtained using teabags with attached trisubstituted dihydroisoquinolones that contain 4-nitrobenzaldeyde group in the R2 position. The teabags were washed with DCM (2 x 50 mL), and shaken with SnCl2 (20 g) in DMF (50 mL, 2 M). After shaking for 24 hours the teabag was washed with DMF (5 x 50 mL), DCM (5 x 50 mL), 5% (v/v) DIEA/DCM (50mL, 2 x 10 minutes), DCM (2 x 50 mL), DMF (2 x 50 mL), MeOH (2 x 50 mL), DCM (4 x 50mL) and allowed to dry.

A solution of benzoic acid (492 mg, 3.75 mmoles), HOBt (507 mg, 3.75 mmoles), and DIC (0.705 mL, 4.5 mmoles) was prepared in DMF (37.5 mL) and added to a resin packet with attached trisubstituted dihydroisoquinolone. After shaking for 16 hours, the teabag was washed with DMF (3 x 30 mL) and DCM (3 x 30 mL). The same coupling procedure was performed on the resulting aniline derived from reduction of the 4-NO_2 of (R2), each being reacted with a separate carboxylic acid from the following (R2) list: propionic acid, butyric acid, cyclohexane carboxylic acid, isobutyric acid, methoxyacetic acid, p-anisic acid, phenylacetic acid, 4-methoxyphenylacetic acid, 2-norbornaneacetic acid, 3,4-dichlorophenylacetic acid, 4-chlorobenzoic acid, valeric acid.

The teabags with attached trisubstituted dihydroisoquinolones were washed with DCM (2 x 50 mL), shaken twice in 55% (v/v) TFA/DCM (30 mL, 30 minutes), then washed with DCM (30 mL), isopropyl alcohol (2 x 30 mL), DCM (2 x 30 mL), 5% (v/v) DIEA/DCM (3 x 30 mL, 2 minutes each) and DCM (3 x 30 mL) and allowed to dry at room temperature. One bag was left as the Boc protected amine (R8 = methyl, after reduction).

A solution of phenylacetic acid (657 mg, 3.75 mmoles), HOBt (507 mg, 3.75 mmoles), and DIC (0.705 mL, 4.5 mmoles) was prepared in DMF (37.5 mL) and added to a resin packet with attached trisubstituted dihydroisoquinolone. After shaking for 16 hours, the teabag was washed with DMF (3 x 30 mL) and DCM (3 x 30 mL). The same coupling procedure was performed on the remaining teabags, each being reacted with a separate carboxylic acid from the list (R8): acetic acid, phenylacetic acid, Boc-glycine, glycine, Boc-alanine, hydroxy acetic acid, Boc-phenylalanine, succinic anhydride, methoxyacetic acid, butyric acid, cyclohexanecarboxylic acid, benzoic acid, 4-bromophenylacetic acid, 4-methoxyphenylacetic acid, 4-chlorobenzoic acid, 4-methoxybenzoic acid, 2-naphthylacetic acid, cyclohexylacetic acid. Additionally, one bag was left non-acylated (R8 = H).

The teabag containing trisubstituted dihydroisoquinoline on resin (R1 = glycine, R2 = benzaldehyde, X =aniline, R8 = phenylacetic acid) was placed in a 50 mL KIMAX glass tube and treated under nitrogen gas with a solution of: 1 M BH_3 in anhydrous tetrahydrofuran (15 mL), boric acid (315 mg) and trimethyl borate (0.5 mL). After the solution's bubbling slowed to a slight fizz, the tube was capped tightly and heated at 65°C for 96 hours. After cooling, the borane solution was decanted and the bag washed with methanol (1x 25 mL), tetrahydrofuran (1 x 25 mL), and again with methanol (4 x 25 mL). During this reaction all carbonyl groups were converted to methylenes and Boc protecting groups were converted to methyl groups.

After drying, the bag was returned to a 50 mL KIMAX glass tube, submerged completely in piperidine, sealed and heated at 65°C for 16 hours. After cooling,

the piperidine was decanted off of the teabag, and the bag was washed with DMF (2 x 25 mL), DCM (2 x 25 mL), methanol (1 x 25 mL), DMF (2 x 25 mL), DCM (2 x 25 mL), and again with methanol (1 x 25 mL) and allowed to dry at room temperature. The remaining teabags were treated in the same manner.

Each teabag prepared above was cleaved separately via standard HF procedures. The isoquinolone was cleaved off of the resin by treatment with HF (5 ml) at -15°C for 9 hrs with the addition of 0.2 ml anisole to each HF cleavage reaction, as a scavenger, followed by warming to room temperature while removing HF with a nitrogen stream. The packet and HF tube were washed with CH_3CN, H_2O, acetic acid (45:45:10) (2 x 5 ml), and the two washes were transferred to a scintillation vial and lyophilized to provide a white crystalline solid.

The isoquinoline compounds were dissolved in an appropriate solvent and tested in a variety of assays. The compounds were characterized by HPLC and mass spectra.

EXAMPLE II

Melanocortin Receptor Assay

This example describes methods for assaying binding to MC receptors.

All cell culture media and reagents were obtained from GibcoBRL (Gaithersburg MD), except for COSMIC CALF SERUM (HyClone; Logan UT). HEK 293 cell lines were transfected with the human MC receptors hMCR-1, hMCR-3, and hMCR-4 (Gantz et al., Biochem. Biophys. Res. Comm. 200:1214-1220 (1994); Gantz et al., J. Biol. Chem. 268:8246-8250 (1993); Gantz et al. J. Biol. Chem.

268:15174-15179 (1993); Haskell-Leuvano et al., Biochem. Biophys. Res. Comm. 204:1137-1142 (1994); each of which is incorporated herein by reference). Vectors for construction of an hMCR-5 expressing cell line were obtained, and a line of HEK 293 cells expressing hMCR-5 was constructed (Gantz, *supra*, 1994). hMCR-5 has been described previously (Franberg et al., Biochem. Biophys. Res. Commun. 236:489-492 (1997); Chowdhary et al., Cytogenet. Cell Genet. 68:1-2 (1995); Chowdhary et al., Cytogenet. Cell Genet. 68:79-81 (1995), each of which is incorporated herein by reference). HEK 293 cells were maintained in DMEM, 25 mM HEPES, 2 mM glutamine, non-essential amino acids, vitamins, sodium pyruvate, 10% COSMIC CALF SERUM, 100 units/ml penicillin, 100 μg/ml streptomycin and 0.2 mg/ml G418 to maintain selection.

Before assaying, cells were washed once with phosphate buffered saline ("PBS"; without Ca^{2+} and Mg^{2+}), and stripped from the flasks using 0.25% trypsin and 0.5 mM EDTA. Cells were suspended in PBS, 10% COSMIC CALF SERUM and 1 mM $CaCl_2$. Cell suspensions were prepared at a density of 2×10^4 cells/ml for HEK 293 cells expressing hMCR-3, hMCR-4 or hMCR-5, and 1×10^5 cells/ml for HEK 293 cells expressing hMCR-1. Suspensions were placed in a water bath and allowed to warm to 37°C for 1 hr.

Binding assays were performed in a total volume of 250 μl for HEK 293 cells. Control and test compounds were dissolved in distilled water. ^{125}I-HP 467 (50,000 dpm) (2000 Ci/mmol) (custom labeled by Amersham; Arlington Heights IL) was prepared in 50 mM Tris, pH 7.4, 2 mg/ml BSA, 10 mM $CaCl_2$, 5 mM $MgCl_2$, 2 mM EDTA and added to each tube. To each tube was added 4×10^3 HEK 293 cells expressing hMCR-3, hMCR-4 or hMCR-5, or 2×10^4 cells

expressing hMCR-1. Assays were incubated for 2.5 hr at 37°C.

GF/B filter plates were prepared by soaking for at least one hour in 5 mg/ml BSA and 10 mM $CaCl_2$. Assays were filtered using a Brandel 96-well cell harvester (Brandel Inc.; Gaithersburg, MD). The filters were washed four times with cold 50 mM Tris, pH 7.4, the filter plates were dehydrated for 2 hr and 35 μl of MICROSCINT was added to each well. Filter plates were counted using a Packard Topcount (Packard Instrument Co.) and data analyzed using GraphPad PRISM v2.0 (GraphPad Software Inc.; San Diego CA) and Microsoft EXCEL v5.0a (Microsoft Corp.; Redmond WA).

To assay isoquinoline compounds, binding assays were performed in duplicate in a 96 well format. HP 467 was prepared in 50 mM Tris, pH 7.4, and ^{125}I-HP 467 was diluted to give 100,000 dpm per 50 μl. An isoquinoline compound, synthesized as described in Example I, was added to the well in 25 μl aliquots. A 25 μl aliquot of ^{125}I-HP 467 was added to each well. A 0.2 ml aliquot of suspended cells was added to each well to give the cell numbers indicate above, and the cells were incubated at 37°C for 2.5 hr. Cells were harvested on GF/B filter plates as described above and counted.

EXAMPLE III

cAMP Assay for Melanocortin Receptors

This example describes methods for assaying cAMP production from G-protein coupled MC receptors.

HEK 293 cells expressing MCR-1, MCR-3, MCR-4 and MCR-5 were used (see Example II). Cells were plated at 20,000 cells per well in a 96-well plate coated with

collagen. The next day, cells were pretreated with 75 μl of 0.4 mM 3-isobutyl-1-methylxanthine (IBMX) in low serum medium containing DMEM, 25 mM HEPES, non-essential amino acids, vitamins, 100 units/ml penicillin, 100 μg/ml streptomycin and 0.1% COSMIC CALF SERUM. IBMX is an inhibitor of cAMP phosphodiesterase. The pretreatment was carried out for 10 min at 37°C.

Following pretreatment, 25 μl of diluted isoquinoline compound was added to the wells, and cells were incubated for 15 min at 37°C. Cells were lysed by adding 25 μl saponin lysis buffer and incubating 2 to 5 min. Plates were covered and stored at -20°C.

cAMP concentration was determined by ELISA. Briefly, 96 well ELISA plates were coated with goat anti-cAMP antibody in PBS for 12 to 72 hr at 4°C. 50 μl of sample was mixed with 50 μl of cAMP ELISA buffer containing 1% bovine serum albumin, 10% heat inactivated donor horse serum, 1% normal mouse serum and 0.05% TWEEN-20 in PBS, and the diluted sample was added to the coated ELISA plate. Standards of known concentrations of cAMP were added to separate wells. 25 μl of 16 ng/ml cAMP-conjugated horse radish peroxidase (HRP) (cAMP-HRP) was added to each well, and the plates were incubated hr at room temperature. Plates were washed and the binding of cAMP-HRP was detected with 3,3',5,5'-tetramethylbenzidine (TMB) and hydrogen peroxide using standard immunoassay procedures.

EXAMPLE IV

Melanocortin Receptor Binding Profile of Isoquinoline Compounds

This example describes MC receptor binding affinity and specificity for various isoquinoline compounds.

Various isoquinoline compounds were tested for *in vitro* binding activity to HEK 293 cells expressing MCR-1 or MCR-4 as described in Example II. Table 1 shows the IC50 values, the concentration giving 50% inhibition of binding of ^{125}I-HP 467, for various isoquinoline compounds. Table 1 also shows for some isoquinoline compounds the percentage of displacement (% Disp.) (in duplicate) of ^{125}I-HP 467 when HEK 293 cells expressing MCR-1 were incubated in the presence of 10 μM isoquinoline compound. As shown in Table 1, isoquinoline compounds exhibited a range of affinities to MCR-1 and MCR-4, including ligands with nM affinities. Some isoquinoline compounds exhibited specificity of about 10-fold for at least one MC receptor over another MC receptor, for example, TRG 2405-241, TRG 2405-252, TRG 2405-253 and TRG 2408-30.

Isoquinoline compounds that are particularly effective MC receptor ligands include TRG 2405-190, TRG 2405-239, TRG 2405-241, TRG 2405-252, TRG 2405-253, TRG 2408-30, TRG 2408-57, TRG 2408-62, TRG 2409-2, TRG 2409-14, TRG 2411-26, TRG 2411-50, TRG 2411-60, TRG 2411-111 and TRG 2411-186, as well as the other ligands described above and claimed below individually.

In describing each compound, Table 1 refers to the starting material used at each position. When describing TRG 2403 to TRG 2413 libraries in Table 1,

"R3" refers to the "X" position. Additionally, in the TRG 2419 and 2420 libraries described in Table 1, two compounds contribute to the "R8" position (and are therefore each designated "R8 in Table 1). The anhydride compound is coupled to the amine compound to form the caroxylic acid of R8. When reduced, the carboxylic acid becomes a substituted alkyl.

	TRG 2403	R8 = BOC			obs.(M+1)	>85%	MC-1	MC-4
Cpd #	R1: Amino Acid	R2: Aldehyde	X: amine	M.W.	M.W.	LCQ	IC50 M	IC50 M
3	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	2-Methoxybenzylamine	516	517	Y	0.5	>10
	TRG 2404							
3	(S)-2,6-Diaminohexanoic acid	4-Bromobenzaldehyde	2-Methoxybenzylamine	552	553	Y	2.5	0.8

	TRG 2405									
	R1= Cyclohexylamine	0R8 = BOC								
									% Disp.	
				prod.	obs.(M+1)	>85%	MC-1	MC-4	MC-1	MC-1
Cpd #	R1: Amino Acids	R2: Aldehydes	R3:amines	MW	M.W.	LCQ	IC50 M	IC50 M	10 uM	10 uM
	Glycine	Benzaldehyde	Cyclohexylamine	364	365	Y			85.3	24.1
2	Glycine	2-Hydroxybenzaldehyde (salicylaldehyde)	Cyclohexylamine	380	381	Y			42.9	40.8
3	Glycine	1,4-Benzodioxan-6-carboxaldehyde	Cyclohexylamine	422	423	Y			46.8	44.2
4	Glycine	1-Methyl-2-pyrrolecarboxaldehyde	Cyclohexylamine	367		N	2.17	11.64	76.8	77.7
5	Glycine	1-Naphthaldehyde	Cyclohexylamine	414	415	Y			53.6	53.8
6	Glycine	2,3,4-Trifluorobenzaldehyde	Cyclohexylamine	418	419	Y			45.7	50
7	Glycine	2,3,5-Trichlorobenzaldehyde	Cyclohexylamine	467	468	Y			50.3	54.8
8	Glycine	2,3-(Methylenedioxy)benzaldehyde	Cyclohexylamine	408	409	Y			0	26.1
9	Glycine	2,3-Difluorobenzaldehyde	Cyclohexylamine	400	401	Y			36.4	33.4
10	Glycine	2,4-Dichlorobenzaldehyde	Cyclohexylamine	433	434	Y			56.9	53
11	Glycine	2,6-Difluorobenzaldehyde	Cyclohexylamine	400	401	Y			45.1	27
12	Glycine	2-Bromobenzaldehyde	Cyclohexylamine	443	444	Y			38.7	41.8
13	Glycine	2-Chloro-5-nitrobenzaldehyde	Cyclohexylamine	414	415	Y			36	32.1
14	Glycine	2-Chloro-6-fluorobenzaldehyde	Cyclohexylamine	417	418	Y			34.2	29.6
15	Glycine	2-Cyanobenzaldehyde	Cyclohexylamine	393	394	Y			23.5	52.5
16	Glycine	2-Fluorobenzaldehyde	Cyclohexylamine	382	383	Y			26.8	40.3
17	Glycine	2-Furaldehyde	Cyclohexylamine	354		N			36	32.8
18	Glycine	2-Imidazolecarboxaldehyde	Cyclohexylamine	354	355	Y			35.9	34.7
19	Glycine	2-Methoxybenzaldehyde (o-anisaldehyde)	Cyclohexylamine	394	395	Y			42.2	36.2
20	Glycine	2-Naphthaldehyde	Cyclohexylamine	414	415	Y			59.8	53.8
21	Glycine	2-Pyridinecarboxaldehyde	Cyclohexylamine	365		N			47.7	42.5

22	Glycine	2-Quinolinecarboxaldehyde	Cyclohexylamine	415		N			29.7	43.4
23	Glycine	2-Thiophenecarboxaldehyde	Cyclohexylamine	370	371	Y			43	47.8
24	Glycine	3,4-(Methylenedioxy)benzaldehyde (piperonal)	Cyclohexylamine	396	397	Y			0	19.4
25	Glycine	3,4-Dibenzyloxybenzaldehyde	Cyclohexylamine	396	397	Y			21.6	31.9
26	Glycine	3,4-Dichlorobenzaldehyde	Cyclohexylamine	433	434	Y			59.6	64.6
27	Glycine	3,4-Difluorobenzaldehyde	Cyclohexylamine	400	401	Y			52.1	43.8
28	Glycine	3,5-Bis(trifluoromethyl)benzaldehyde	Cyclohexylamine	500	501	Y	8.75	9.24	52	52.5
29	Glycine	3,5-Dibenzyloxybenzaldehyde	Cyclohexylamine	396	397	Y			28.5	26.2
30	Glycine	3,5-Dichlorobenzaldehyde	Cyclohexylamine	433	434	Y			54.7	52.8
31	Glycine	3,5-Dimethoxybenzaldehyde	Cyclohexylamine	424	425	Y			40.7	48.5
32	Glycine	3,5-Dimethyl-4-hydroxybenzaldehyde	Cyclohexylamine	408	409	Y			10.1	38.3
33	Glycine	3-(3,4-Dichlorophenoxy)benzaldehyde	Cyclohexylamine	525	526	Y			54.2	48.7
34	Glycine	3-(4-Methoxyphenoxy)benzaldehyde	Cyclohexylamine	486	487	Y			55.6	56.1
35	Glycine	3-(Trifluoromethyl)benzaldehyde	Cyclohexylamine	432	433	Y			54.6	55
36	Glycine	3-Bromo-4-fluorobenzaldehyde	Cyclohexylamine	461	462	Y			51.8	53.6
37	Glycine	3-Bromobenzaldehyde	Cyclohexylamine	443	444	Y			49.7	54.4
38	Glycine	3-Carboxybenzaldehyde	Cyclohexylamine	476	477	Y			35.2	39.2
39	Glycine	3-Cyanobenzaldehyde	Cyclohexylamine	393	394	Y			23.2	16.9
40	Glycine	3-Fluoro-4-methoxybenzaldehyde	Cyclohexylamine	412	413	Y			22.4	35.5

41	Glycine	3-Fluorobenzaldehyde	Cyclohexylamine	382	383	Y			19.6	19.8
42	Glycine	3-Furaldehyde	Cyclohexylamine	354		N			43.6	40.7
43	Glycine	3-Hydroxybenzaldehyde	Cyclohexylamine	380	381	Y			32.3	23.1
44	Glycine	3-Methoxy-4-hydroxy-5-nitrobenzaldehyde	Cyclohexylamine	425	426	Y			35.4	22
45	Glycine	3-Methoxybenzaldehyde (m-anisaldehyde)	Cyclohexylamine	394	395	Y			40.6	31.9
46	Glycine	3-Methyl-4-methoxybenzaldehyde	Cyclohexylamine	408	409	Y			46.8	40.3
47	Glycine	3-Methylbenzaldehyde (m-tolualdehyde)	Cyclohexylamine	378	379	Y	14.30	18.93	42.3	45.8
48	Glycine	3-Nitro-4-chlorobenzaldehyde	Cyclohexylamine	414	415	Y			20.5	50.8
49	Glycine	3-Nitrobenzaldehyde	Cyclohexylamine	409	410	Y			37.2	42.4
50	Glycine	3-Phenoxybenzaldehyde	Cyclohexylamine	456	457	Y			61.9	50.8
51	Glycine	3-Pyridinecarboxaldehyde	Cyclohexylamine	365		N			30.6	23.1
52	Glycine	3-Quinolinecarboxaldehyde	Cyclohexylamine	415		N			42.4	42.3
53	Glycine	3-Thiophenecarboxaldehyde	Cyclohexylamine	370	371	Y			43.3	43.4
54	Glycine	4-(3-Dimethylaminopropoxy)benzaldehyde	Cyclohexylamine	465	466	Y			1.3	9
55	Glycine	4-(Dimethylamino)benzaldehyde	Cyclohexylamine	407	408	Y			32.6	38.1
56	Glycine	4-(Methylcarboxylate)benzaldehyde	Cyclohexylamine	484	485	Y			35.3	43.6
57	Glycine	4-(Methylthio)benzaldehyde	Cyclohexylamine	410	411	Y			17.4	42.8
58	Glycine	4-(Trifluoromethyl)benzaldehyde	Cyclohexylamine	432	433	Y			56.3	46.6
59	Glycine	4-Acetamidobenzaldehyde	Cyclohexylamine	407	408	Y			34.3	40.1
60	Glycine	4-Methoxybenzaldehyde (p-anisaldehyde)	Cyclohexylamine	394	395	Y			41.4	42.4
61	Glycine	4-Biphenylcarboxaldehyde	Cyclohexylamine	440	441	Y			54.7	61.9
62	Glycine	4-Bromobenzaldehyde	Cyclohexylamine	443	444	Y			32.1	54.3
63	Glycine	4-Carboxybenzaldehyde	Cyclohexylamine	476	477	Y			41.6	49.1
64	Glycine	4-Cyanobenzaldehyde	Cyclohexylamine	393	394	Y			0	0
65	Glycine	4-Fluorobenzaldehyde	Cyclohexylamine	382	383	Y			49.6	33.9
66	Glycine	4-Hydroxybenzaldehyde	Cyclohexylamine	380	381	Y			81.6	11.3
67	Glycine	4-Isopropylbenzaldehyde	Cyclohexylamine	406	407	Y			54	51.3
68	Glycine	4-Methoxy-1-naphthaldehyde	Cyclohexylamine	444	445	Y			55.3	52.3

69	Glycine	4-Methylbenzaldehyde (p-tolualdehyde)	Cyclohexylamine	378	379	Y			49.8	49
70	Glycine	3-Hydroxy-4-nitrobenzaldehyde	Cyclohexylamine	425		N			19.9	46.7
71	Glycine	4-Nitrobenzaldehyde	Cyclohexylamine	409	410	Y			28.2	40
72	Glycine	4-Phenoxybenzaldehyde	Cyclohexylamine	456	457	Y			50.1	57.7
73	Glycine	4-Propoxybenzaldehyde	Cyclohexylamine	422	423	Y			60.1	60.5
74	Glycine	4-Pyridinecarboxaldehyde	Cyclohexylamine	365	366	Y			35.3	0
75	Glycine	4-Quinolinecarboxaldehyde	Cyclohexylamine	415		N			38.9	17.6
76	Glycine	5-(Hydroxymethyl)-2-furaldehyde	Cyclohexylamine	474		N			22.8	32.7
77	Glycine	3-Methoxy-4-hydroxy-5-bromobenzaldehyde	Cyclohexylamine	477	478	Y	4.21	>10	61.3	67.9
78	Glycine	5-Methyl-2-thiophenecarboxaldehyde	Cyclohexylamine	384		N			33.3	40.8
79	Glycine	5-Methyl-2-furaldehyde (5-methylfurfural)	Cyclohexylamine	368		N			17.3	26.3
80	Glycine	5-Nitro-2-furaldehyde	Cyclohexylamine	399		N	8.66	20.81	30.8	52.9
81	Glycine	6-Methyl-2-pyridinecarboxaldehyde	Cyclohexylamine	379		N			0	43.1
82	Glycine	8-Hydroxyquinoline-2-carboxaldehyde	Cyclohexylamine	431		N			18.5	29.6
83	Glycine	9-Ethyl-3-carbazolecarboxaldehyde	Cyclohexylamine	481	482	Y			39.1	46.9
84	Glycine	9-Formyl-8-hydroxyjulolidine	Cyclohexylamine	475		N			18.2	37.5
85	Glycine	Pyrrole-2-carboxaldehyde	Cyclohexylamine	353		N	5.98	33.47	57.1	59.8

86	Glycine	3-Hydroxy-4-methoxybenzaldehyde	Cyclohexylamine	396	397	Y			12.9	31.6
87	Glycine	4-Methylsulphonylbenzaldehyde	Cyclohexylamine	442	443	Y			21.9	22.1
88	Glycine	4-Methoxy-3-(sulfonic acid, Na)benzaldehyde	Cyclohexylamine	474	475	Y			5.5	0
89	Glycine	5-Bromo-2-furaldehyde	Cyclohexylamine	433	434	Y			21.5	31.2
90	Glycine	2-Thiazolecarboxaldehyde	Cyclohexylamine	371		N			48.4	45.9
91	(S)-2,3-Diaminopropionic acid	Benzaldehyde	Cyclohexylamine	407	408	Y			35.2	43.9
92	(S)-2,3-Diaminopropionic acid	2-Hydroxybenzaldehyde (salicylaldehyde)	Cyclohexylamine	423	424	Y			57.6	49.9
93	(S)-2,3-Diaminopropionic acid	1,4-Benzodioxan-6-carboxaldehyde	Cyclohexylamine	465	466	Y			43.2	56.2
94	(S)-2,3-Diaminopropionic acid	1-Methyl-2-pyrrolecarboxaldehyde	Cyclohexylamine	410		N	2.11	10.46	68.9	72
95	(S)-2,3-Diaminopropionic acid	1-Naphthaldehyde	Cyclohexylamine	457	458	Y			45.6	51.1
96	(S)-2,3-Diaminopropionic acid	2,3,4-Trifluorobenzaldehyde	Cyclohexylamine	461	462	Y			44.5	54.4
97	(S)-2,3-Diaminopropionic acid	2,3,5-Trichlorobenzaldehyde	Cyclohexylamine	510	511	Y			58.2	61.1
98	(S)-2,3-Diaminopropionic acid	2,3-(Methylenedioxy)benzaldehyde	Cyclohexylamine	451	452	Y			20.1	48.3
99	(S)-2,3-Diaminopropionic acid	2,3-Difluorobenzaldehyde	Cyclohexylamine	443	444	Y			34.7	54.2
100	(S)-2,3-Diaminopropionic acid	2,4-Dichlorobenzaldehyde	Cyclohexylamine	476	477	Y	12.18	11.22	54.2	59.6
101	(S)-2,3-Diaminopropionic acid	2,6-Difluorobenzaldehyde	Cyclohexylamine	443	444	Y			34	45.3
102	(S)-2,3-Diaminopropionic acid	2-Bromobenzaldehyde	Cyclohexylamine	486	487	Y			44.7	50.4
103	(S)-2,3-Diaminopropionic acid	2-Chloro-5-nitrobenzaldehyde	Cyclohexylamine	457	458	Y			44.6	45.2
104	(S)-2,3-Diaminopropionic acid	2-Chloro-6-fluorobenzaldehyde	Cyclohexylamine	460	461	Y			32.8	33.3
105	(S)-2,3-Diaminopropionic acid	2-Cyanobenzaldehyde	Cyclohexylamine	436	437	Y			20.2	49.9
106	(S)-2,3-Diaminopropionic acid	2-Fluorobenzaldehyde	Cyclohexylamine	425	426	Y			40.7	44.7

107	(S)-2,3-Diaminopropionic acid	2-Furaldehyde	Cyclohexylamine	397		N			43.1	52.1
108	(S)-2,3-Diaminopropionic acid	2-Imidazolecarboxaldehyde	Cyclohexylamine	397	398	Y			46	46.6
109	(S)-2,3-Diaminopropionic acid	2-Methoxybenzaldehyde (o-anisaldehyde)	Cyclohexylamine	437	438	Y			34.7	44.7
110	(S)-2,3-Diaminopropionic acid	2-Naphthaldehyde	Cyclohexylamine	457	458	Y			59.5	61.6
111	(S)-2,3-Diaminopropionic acid	2-Pyridinecarboxaldehyde	Cyclohexylamine	408		N	7.48	17.13	57.2	51
112	(S)-2,3-Diaminopropionic acid	2-Quinolinecarboxaldehyde	Cyclohexylamine	458		N			42.2	43.2
113	(S)-2,3-Diaminopropionic acid	2-Thiophenecarboxaldehyde	Cyclohexylamine	413	414	Y			40	58.5
114	(S)-2,3-Diaminopropionic acid	3,4-(Methylenedioxy)benzaldehyde (piperonal)	Cyclohexylamine	439	440	Y			30.6	40.9
115	(S)-2,3-Diaminopropionic acid	3,4-Dibenzyloxybenzaldehyde	Cyclohexylamine	439	440	Y			20.6	22.1
116	(S)-2,3-Diaminopropionic acid	3,4-Dichlorobenzaldehyde	Cyclohexylamine	476	477	Y			62.3	63
117	(S)-2,3-Diaminopropionic acid	3,4-Difluorobenzaldehyde	Cyclohexylamine	443	444	Y			40.9	55.7
118	(S)-2,3-Diaminopropionic acid	3,5-Bis(trifluoromethyl)benzaldehyde	Cyclohexylamine	543	544	Y			47.3	58.9
119	(S)-2,3-Diaminopropionic acid	3,5-Dibenzyloxybenzaldehyde	Cyclohexylamine	439	440	Y			25.9	39.8
120	(S)-2,3-Diaminopropionic acid	3,5-Dichlorobenzaldehyde	Cyclohexylamine	476	477	Y			52.4	54.3
121	(S)-2,3-Diaminopropionic acid	3,5-Dimethoxybenzaldehyde	Cyclohexylamine	467	468	Y			35.2	38.7
122	(S)-2,3-Diaminopropionic acid	3,5-Dimethyl-4-hydroxybenzaldehyde	Cyclohexylamine	451	452	Y			17.6	40.7
123	(S)-2,3-Diaminopropionic acid	3-(3,4-Dichlorophenoxy)benzaldehyde	Cyclohexylamine	568	569	Y			47.9	55.6
124	(S)-2,3-Diaminopropionic acid	3-(4-Methoxyphenoxy)benzaldehyde	Cyclohexylamine	529	530	Y	5.16	3.1	65.2	63
125	(S)-2,3-Diaminopropionic acid	3-(Trifluoromethyl)benzaldehyde	Cyclohexylamine	475	476	Y			59.1	58.4
126	(S)-2,3-Diaminopropionic acid	3-Bromo-4-fluorobenzaldehyde	Cyclohexylamine	504	505	Y	5.34	12.82	52.4	58.74

127	(S)-2,3-Diaminopropionic acid	3-Bromobenzaldehyde	Cyclohexylamine	486	487	Y			50.6	60.3
128	(S)-2,3-Diaminopropionic acid	3-Carboxybenzaldehyde	Cyclohexylamine	519	520	Y			52.9	54
129	(S)-2,3-Diaminopropionic acid	3-Cyanobenzaldehyde	Cyclohexylamine	436	437	Y			39.8	39.6
130	(S)-2,3-Diaminopropionic acid	3-Fluoro-4-methoxybenzaldehyde	Cyclohexylamine	455	456	Y			48.9	43.3

131	(S)-2,3-Diaminopropionic acid	3-Fluorobenzaldehyde	Cyclohexylamine	425	426	Y			39.2	55.7
132	(S)-2,3-Diaminopropionic acid	3-Furaldehyde	Cyclohexylamine	397		N			51.8	51.7
133	(S)-2,3-Diaminopropionic acid	3-Hydroxybenzaldehyde	Cyclohexylamine	423	424	Y	20.01	12.40	37.7	44.1
134	(S)-2,3-Diaminopropionic acid	3-Methoxy-4-hydroxy-5-nitrobenzaldehyde	Cyclohexylamine	468	469	Y			43.4	48
135	(S)-2,3-Diaminopropionic acid	3-Methoxybenzaldehyde (m-anisaldehyde)	Cyclohexylamine	437	438	Y			43.9	39.7
136	(S)-2,3-Diaminopropionic acid	3-Methyl-4-methoxybenzaldehyde	Cyclohexylamine	451	452	Y			49	51.8
137	(S)-2,3-Diaminopropionic acid	3-Methylbenzaldehyde (m-tolualdehyde)	Cyclohexylamine	421	422	Y			40.6	46
138	(S)-2,3-Diaminopropionic acid	3-Nitro-4-chlorobenzaldehyde	Cyclohexylamine	457	458	Y			53.2	56.1
139	(S)-2,3-Diaminopropionic acid	3-Nitrobenzaldehyde	Cyclohexylamine	452	453	Y			40.3	45.5
140	(S)-2,3-Diaminopropionic acid	3-Phenoxybenzaldehyde	Cyclohexylamine	499	500	Y			67.6	67.8
141	(S)-2,3-Diaminopropionic acid	3-Pyridinecarboxaldehyde	Cyclohexylamine	408		N			15	16.2
142	(S)-2,3-Diaminopropionic acid	3-Quinolinecarboxaldehyde	Cyclohexylamine	458		N			48.5	45.1
143	(S)-2,3-Diaminopropionic acid	3-Thiophenecarboxaldehyde	Cyclohexylamine	413	414	Y			54.6	50.4
144	(S)-2,3-Diaminopropionic acid	4-(3-Dimethylaminopropoxy)benzaldehyde	Cyclohexylamine	508	509	Y			29.6	41.7
145	(S)-2,3-Diaminopropionic acid	4-(Dimethylamino)benzaldehyde	Cyclohexylamine	450	451	Y			41.2	49.7
146	(S)-2,3-Diaminopropionic acid	4-(Methylcarboxylate)benzaldehyde	Cyclohexylamine	527	528	Y			59.5	60.1
147	(S)-2,3-Diaminopropionic acid	4-(Methylthio)benzaldehyde	Cyclohexylamine	453	454	Y			31.6	38.9
148	(S)-2,3-Diaminopropionic acid	4-(Trifluoromethyl)benzaldehyde	Cyclohexylamine	475	476	Y	10.29	8.95	63.7	57.4
149	(S)-2,3-Diaminopropionic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	450	451	Y			30.1	52.3
150	(S)-2,3-Diaminopropionic acid	4-Methoxybenzaldehyde (p-anisaldehyde)	Cyclohexylamine	437	438	Y			37.6	54.7

151	(S)-2,3-Diaminopropionic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	483	484	Y			61.5	57.6
152	(S)-2,3-Diaminopropionic acid	4-Bromobenzaldehyde	Cyclohexylamine	486	487	Y			52.8	52.9
153	(S)-2,3-Diaminopropionic acid	4-Carboxybenzaldehyde	Cyclohexylamine	519	520	Y			42.1	58.6
154	(S)-2,3-Diaminopropionic acid	4-Cyanobenzaldehyde	Cyclohexylamine	436	437	Y			43.1	54.8
155	(S)-2,3-Diaminopropionic acid	4-Fluorobenzaldehyde	Cyclohexylamine	425	426	Y			52.3	55.6
156	(S)-2,3-Diaminopropionic acid	4-Hydroxybenzaldehyde	Cyclohexylamine	423	424	Y	16.96	20.59	25.9	21.3
157	(S)-2,3-Diaminopropionic acid	4-Isopropylbenzaldehyde	Cyclohexylamine	449	450	Y			58.4	56.1
158	(S)-2,3-Diaminopropionic acid	4-Methoxy-1-naphthaldehyde	Cyclohexylamine	487	488	Y			45.6	45.8
159	(S)-2,3-Diaminopropionic acid	4-Methylbenzaldehyde (p-tolualdehyde)	Cyclohexylamine	421	422	Y			51	53.5
160	(S)-2,3-Diaminopropionic acid	3-Hydroxy-4-nitrobenzaldehyde	Cyclohexylamine	468	469	Y			26.1	41.7
161	(S)-2,3-Diaminopropionic acid	4-Nitrobenzaldehyde	Cyclohexylamine	452	453	Y			58.4	59.1
162	(S)-2,3-Diaminopropionic acid	4-Phenoxybenzaldehyde	Cyclohexylamine	499	500	Y			71	59.6
163	(S)-2,3-Diaminopropionic acid	4-Propoxybenzaldehyde	Cyclohexylamine	465	466	Y			62.4	58.1
164	(S)-2,3-Diaminopropionic acid	4-Pyridinecarboxaldehyde	Cyclohexylamine	408	409	Y			24.7	33.5
165	(S)-2,3-Diaminopropionic acid	4-Quinolinecarboxaldehyde	Cyclohexylamine	458		N			37.3	34.6
166	(S)-2,3-Diaminopropionic acid	5-(Hydroxymethyl)-2-furaldehyde	Cyclohexylamine	517		N			38.9	41.8
167	(S)-2,3-Diaminopropionic acid	3-Methoxy-4-hydroxy-5-bromobenzaldehyde	Cyclohexylamine	520	521	Y	18.27	>10	35.1	24.2
168	(S)-2,3-Diaminopropionic acid	5-Methyl-2-thiophenecarboxaldehyde	Cyclohexylamine	427	428	Y			44.9	24.1
169	(S)-2,3-Diaminopropionic acid	5-Methyl-2-furaldehyde (5-methylfurfural)	Cyclohexylamine	411		N			62.2	51.5
170	(S)-2,3-Diaminopropionic acid	5-Nitro-2-furaldehyde	Cyclohexylamine	442		N	4.81	10.17	68.4	57.5
171	(S)-2,3-Diaminopropionic acid	6-Methyl-2-pyridinecarboxaldehyde	Cyclohexylamine	422		N			63.1	49.7

172	(S)-2,3-Diaminopropionic acid	8-Hydroxyquinoline-2-carboxaldehyde	Cyclohexylamine	474	475	Y	10.82	>10	59.4	43.9
173	(S)-2,3-Diaminopropionic acid	9-Ethyl-3-carbazolecarboxaldehyde	Cyclohexylamine	524	525	Y			67	59.3
174	(S)-2,3-Diaminopropionic acid	9-Formyl-8-hydroxyjulolidine	Cyclohexylamine	518		N			41.9	38.8
175	(S)-2,3-Diaminopropionic acid	Pyrrole-2-carboxaldehyde	Cyclohexylamine	396		N	5.86	15.75	68.5	58.8

176	(S)-2,3-Diaminopropionic acid	3-Hydroxy-4-methoxybenzaldehyde	Cyclohexylamine	439	440	Y			26.1	19.3
177	(S)-2,3-Diaminopropionic acid	4-Methylsulphonylbenzaldehyde	Cyclohexylamine	485	486	Y			39	30.7
178	(S)-2,3-Diaminopropionic acid	4-Methoxy-3-(sulfonic acid, Na)benzaldehyde	Cyclohexylamine	517	518	Y			25	22.1
179	(S)-2,3-Diaminopropionic acid	5-Bromo-2-furaldehyde	Cyclohexylamine	476	477	Y			61.1	56.8
180	(S)-2,3-Diaminopropionic acid	2-Thiazolecarboxaldehyde	Cyclohexylamine	414		N	3.88	10.83	72	64.6
181	(S)-2,6-Diaminohexanoic acid	Benzaldehyde	Cyclohexylamine	449	450	Y			57.3	64.4
182	(S)-2,6-Diaminohexanoic acid	2-Hydroxybenzaldehyde (salicylaldehyde)	Cyclohexylamine	465	466	Y			37.5	44.4
183	(S)-2,6-Diaminohexanoic acid	1,4-Benzodioxan-6-carboxaldehyde	Cyclohexylamine	507	508	Y			58.9	64.1
184	(S)-2,6-Diaminohexanoic acid	1-Methyl-2-pyrrolecarboxaldehyde	Cyclohexylamine	452	453	Y			55.8	46
185	(S)-2,6-Diaminohexanoic acid	1-Naphthaldehyde	Cyclohexylamine	499	500	Y			68.1	60.4
186	(S)-2,6-Diaminohexanoic acid	2,3,4-Trifluorobenzaldehyde	Cyclohexylamine	503	504	Y			62.7	52.7
187	(S)-2,6-Diaminohexanoic acid	2,3,5-Trichlorobenzaldehyde	Cyclohexylamine	552	553	Y			64.6	59.3
188	(S)-2,6-Diaminohexanoic acid	2,3-(Methylenedioxy)benzaldehyde	Cyclohexylamine	493	494	Y			66.9	60.1
189	(S)-2,6-Diaminohexanoic acid	2,3-Difluorobenzaldehyde	Cyclohexylamine	485	486	Y			45	54.6.
190	(S)-2,6-Diaminohexanoic acid	2,4-Dichlorobenzaldehyde	Cyclohexylamine	518	519	Y	1.20	1.87	79.4	81
191	(S)-2,6-Diaminohexanoic acid	2,6-Difluorobenzaldehyde	Cyclohexylamine	485	486	Y			41.2	47.3
192	(S)-2,6-Diaminohexanoic acid	2-Bromobenzaldehyde	Cyclohexylamine	528	529	Y			73.8	50.9
193	(S)-2,6-Diaminohexanoic acid	2-Chloro-5-nitrobenzaldehyde	Cyclohexylamine	499	500	Y			54.8	54.6
194	(S)-2,6-Diaminohexanoic acid	2-Chloro-6-fluorobenzaldehyde	Cyclohexylamine	502	503	Y			50.7	51.4
195	(S)-2,6-Diaminohexanoic acid	2-Cyanobenzaldehyde	Cyclohexylamine	478	479	Y			44.7	35.7

196	(S)-2,6-Diaminohexanoic acid	2-Fluorobenzaldehyde	Cyclohexylamine	467	468	Y			69.1	64.6
197	(S)-2,6-Diaminohexanoic acid	2-Furaldehyde	Cyclohexylamine	439		N			41.9	41.3
198	(S)-2,6-Diaminohexanoic acid	2-Imidazolecarboxaldehyde	Cyclohexylamine	439	440	Y			65.4	26.4
199	(S)-2,6-Diaminohexanoic acid	2-Methoxybenzaldehyde (o-anisaldehyde)	Cyclohexylamine	479	480	Y	2.79	5.83	71.5	71.4
200	(S)-2,6-Diaminohexanoic acid	2-Naphthaldehyde	Cyclohexylamine	499	500	Y	1.78	2.10	83.6	81
201	(S)-2,6-Diaminohexanoic acid	2-Pyridinecarboxaldehyde	Cyclohexylamine	450		N			61.1	43.4
202	(S)-2,6-Diaminohexanoic acid	2-Quinolinecarboxaldehyde	Cyclohexylamine	500		N			63	53.2
203	(S)-2,6-Diaminohexanoic acid	2-Thiophenecarboxaldehyde	Cyclohexylamine	455	456	Y			58.1	49
204	(S)-2,6-Diaminohexanoic acid	3,4-(Methylenedioxy)benzaldehyde (piperonal)	Cyclohexylamine	481	482	Y			32.1	25.8
205	(S)-2,6-Diaminohexanoic acid	3,4-Dibenzyloxybenzaldehyde	Cyclohexylamine	481	482	Y			35.9	39
206	(S)-2,6-Diaminohexanoic acid	3,4-Dichlorobenzaldehyde	Cyclohexylamine	518	519	Y	2.70	1.35	75	69
207	(S)-2,6-Diaminohexanoic acid	3,4-Difluorobenzaldehyde	Cyclohexylamine	485	486	Y	3.99	3.16	65	65.5
208	(S)-2,6-Diaminohexanoic acid	3,5-Bis(trifluoromethyl)benzaldehyde	Cyclohexylamine	585	586	Y	3.34	2.99	79.5	67.5
209	(S)-2,6-Diaminohexanoic acid	3,5-Dibenzyloxybenzaldehyde	Cyclohexylamine	481	482	Y			19.7	24.3
210	(S)-2,6-Diaminohexanoic acid	3,5-Dichlorobenzaldehyde	Cyclohexylamine	518	519	Y			76.5	69.6
211	(S)-2,6-Diaminohexanoic acid	3,5-Dimethoxybenzaldehyde	Cyclohexylamine	509	510	Y			69.9	69
212	(S)-2,6-Diaminohexanoic acid	3,5-Dimethyl-4-hydroxybenzaldehyde	Cyclohexylamine	493	494	Y			54.8	45.8
213	(S)-2,6-Diaminohexanoic acid	3-(3,4-Dichlorophenoxy)benzaldehyde	Cyclohexylamine	610	611	Y			80	78.1
214	(S)-2,6-Diaminohexanoic acid	3-(4-Methoxyphenoxy)benzaldehyde	Cyclohexylamine	571	572	Y			87.5	84.9
215	(S)-2,6-Diaminohexanoic acid	3-(Trifluoromethyl)benzaldehyde	Cyclohexylamine	517	518	Y	2.76	6.36	75.9	70.8
216	(S)-2,6-Diaminohexanoic acid	3-Bromo-4-fluorobenzaldehyde	Cyclohexylamine	546	547	Y	2.41	3.73	78.9	67.9

217	(S)-2,6-Diaminohexanoic acid	3-Bromobenzaldehyde	Cyclohexylamine	528	529	Y			74.5	688
218	(S)-2,6-Diaminohexanoic acid	3-Carboxybenzaldehyde	Cyclohexylamine	561	562	Y			61.4	57.2
219	(S)-2,6-Diaminohexanoic acid	3-Cyanobenzaldehyde	Cyclohexylamine	478	479	Y			43.5	42.9
220	(S)-2,6-Diaminohexanoic acid	3-Fluoro-4-methoxybenzaldehyde	Cyclohexylamine	497	498	Y			67.3	60.6

221	(S)-2,6-Diaminohexanoic acid	3-Fluorobenzaldehyde	Cyclohexylamine	467	468	Y	3.91	5.46	65.2	62.7
222	(S)-2,6-Diaminohexanoic acid	3-Furaldehyde	Cyclohexylamine	439		N			34.3	39.3
223	(S)-2,6-Diaminohexanoic acid	3-Hydroxybenzaldehyde	Cyclohexylamine	465	466	Y	20.92	>10	33.6	21.2
224	(S)-2,6-Diaminohexanoic acid	3-Methoxy-4-hydroxy-5-nitrobenzaldehyde	Cyclohexylamine	510	511	Y			54.6	36.6
225	(S)-2,6-Diaminohexanoic acid	3-Methoxybenzaldehyde (m-anisaldehyde)	Cyclohexylamine	479	480	Y			69.8	69.4
226	(S)-2,6-Diaminohexanoic acid	3-Methyl-4-methoxybenzaldehyde	Cyclohexylamine	493	494	Y	3.84	13.68	79.1	77.7
227	(S)-2,6-Diaminohexanoic acid	3-Methylbenzaldehyde (m-tolualdehyde)	Cyclohexylamine	463	464	Y	1.55	5.59	78.2	74.6
228	(S)-2,6-Diaminohexanoic acid	3-Nitro-4-chlorobenzaldehyde	Cyclohexylamine	499	500	Y			78.5	69.3
229	(S)-2,6-Diaminohexanoic acid	3-Nitrobenzaldehyde	Cyclohexylamine	494	495	Y			58.6	48.8
230	(S)-2,6-Diaminohexanoic acid	3-Phenoxybenzaldehyde	Cyclohexylamine	541	542	Y	2.12	3.88	89.2	84.2
231	(S)-2,6-Diaminohexanoic acid	3-Pyridinecarboxaldehyde	Cyclohexylamine	450	451	Y			25	18.9
232	(S)-2,6-Diaminohexanoic acid	3-Quinolinecarboxaldehyde	Cyclohexylamine	500		N			36.1	34.2
233	(S)-2,6-Diaminohexanoic acid	3-Thiophenecarboxaldehyde	Cyclohexylamine	455	456	Y			53.6	42.8
234	(S)-2,6-Diaminohexanoic acid	4-(3-Dimethylaminopropoxy) benzaldehyde	Cyclohexylamine	550	551	Y			52.9	37.7
235	(S)-2,6-Diaminohexanoic acid	4-(Dimethylamino)benzaldehyde	Cyclohexylamine	492	493	Y	5.91	11.04	64.2	26.3
236	(S)-2,6-Diaminohexanoic acid	4-(Methylcarboxylate) benzaldehyde	Cyclohexylamine	569	570	Y			75.7	69.7
237	(S)-2,6-Diaminohexanoic acid	4-(Methylthio)benzaldehyde	Cyclohexylamine	495	496	Y			62.2	47.8
238	(S)-2,6-Diaminohexanoic acid	4-(Trifluoromethyl)benzaldehyde	Cyclohexylamine	517	518	Y	2.54	retest	76.8	72.8
239	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	492	493	Y	0.58	49.70	86.6	85.2
240	(S)-2,6-Diaminohexanoic acid	4-Methoxybenzaldehyde (p-anisaldehyde)	Cyclohexylamine	479	480	Y	3.16	12.49	69.6	66.5

241	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	525	526	Y	1.11	10.07	89.5	88.8
242	(S)-2,6-Diaminohexanoic acid	4-Bromobenzaldehyde	Cyclohexylamine	528	529	Y	2.12	0.69	86	83.4
243	(S)-2,6-Diaminohexanoic acid	4-Carboxybenzaldehyde	Cyclohexylamine	561	562	Y			42	47.9
244	(S)-2,6-Diaminohexanoic acid	4-Cyanobenzaldehyde	Cyclohexylamine	478	479	Y			29.7	22.5
245	(S)-2,6-Diaminohexanoic acid	4-Fluorobenzaldehyde	Cyclohexylamine	467	468	Y	6.64	4.72	56.6	56.8
246	(S)-2,6-Diaminohexanoic acid	4-Hydroxybenzaldehyde	Cyclohexylamine	465	466	Y	48.11	>10	26.5	20.7
247	(S)-2,6-Diaminohexanoic acid	4-Isopropylbenzaldehyde	Cyclohexylamine	491	492	Y	1.59	8.66	83	85.3
248	(S)-2,6-Diaminohexanoic acid	4-Methoxy-1-naphthaldehyde	Cyclohexylamine	529	530	Y			56.5	67.9
249	(S)-2,6-Diaminohexanoic acid	4-Methylbenzaldehyde (p-tolualdehyde)	Cyclohexylamine	463	464	Y	1.29	1.87	82.3	83
250	(S)-2,6-Diaminohexanoic acid	3-Hydroxy-4-nitrobenzaldehyde	Cyclohexylamine	510	511	Y			34.7	50.5
251	(S)-2,6-Diaminohexanoic acid	4-Nitrobenzaldehyde	Cyclohexylamine	494	495	Y	13.17	10.52	49.4	46.9
252	(S)-2,6-Diaminohexanoic acid	4-Phenoxybenzaldehyde	Cyclohexylamine	541	542	Y	0.58	7.04	95.1	95.5
253	(S)-2,6-Diaminohexanoic acid	4-Propoxybenzaldehyde	Cyclohexylamine	507	508	Y	0.73	13.05	93.9	92.2
254	(S)-2,6-Diaminohexanoic acid	4-Pyridinecarboxaldehyde	Cyclohexylamine	450	451	Y			24.9	29.1
255	(S)-2,6-Diaminohexanoic acid	4-Quinolinecarboxaldehyde	Cyclohexylamine	500		N			29.2	25.3
256	(S)-2,6-Diaminohexanoic acid	5-(Hydroxymethyl)-2-furaldehyde	Cyclohexylamine	559		N			38.9	38.9
257	(S)-2,6-Diaminohexanoic acid	3-Methoxy-4-hydroxy-5-bromobenzaldehyde	Cyclohexylamine	562	563	Y	>10	>10	26.3	28.4
258	(S)-2,6-Diaminohexanoic acid	5-Methyl-2-thiophenecarboxaldehyde	Cyclohexylamine	469	470	Y	2.42	5.41	80.7	81.9
259	(S)-2,6-Diaminohexanoic acid	5-Methyl-2-furaldehyde (5-methylfurfural)	Cyclohexylamine	453	454	Y	7.27	15.59	42.5	48.1
260	(S)-2,6-Diaminohexanoic acid	5-Nitro-2-furaldehyde	Cyclohexylamine	484		N			43	39
261	(S)-2,6-Diaminohexanoic acid	6-Methyl-2-pyridinecarboxaldehyde	Cyclohexylamine	464		N			48.9	47.8

262	(S)-2,6-Diaminohexanoic acid	8-Hydroxyquinoline-2-carboxaldehyde	Cyclohexylamine	516	517	Y	4.17	>10	66.1	66.8
263	(S)-2,6-Diaminohexanoic acid	9-Ethyl-3-carbazolecarboxaldehyde	Cyclohexylamine	566	567	Y			61.6	65.3
264	(S)-2,6-Diaminohexanoic acid	9-Formyl-8-hydroxyjulolidine	Cyclohexylamine	560	561	Y			35	39.4
265	(S)-2,6-Diaminohexanoic acid	Pyrrole-2-carboxaldehyde	Cyclohexylamine	438	439	Y			60.5	54.1

266	(S)-2,6-Diaminohexanoic acid	3-Hydroxy-4-methoxybenzaldehyde	Cyclohexylamine	481	482	Y	>10	>10	36.4	31.8
267	(S)-2,6-Diaminohexanoic acid	4-Methylsulphonylbenzaldehyde	Cyclohexylamine	527	528	Y			21.5	8.4
268	(S)-2,6-Diaminohexanoic acid	4-Methoxy-3-(sulfonic acid, Na)benzaldehyde	Cyclohexylamine	559	560	Y			0	3.6
269	(S)-2,6-Diaminohexanoic acid	5-Bromo-2-furaldehyde	Cyclohexylamine	518	519	Y			55.9	57.7
270	(S)-2,6-Diaminohexanoic acid	2-Thiazolecarboxaldehyde	Cyclohexylamine	456		N			41.1	33.7

	TRG 2406	R8 = BOC						
					obs.(M+1)	>85%	MC-1	MC-4
Cmpd #	R1: Amino Acids	R2: Aldehydes	X: amines	M.W.	M.W.	LCQ	IC50 M	IC50 M
1	(S)-2,6-Diaminohexanoic acid	1-Methyl-2-pyrrolecarboxaldehyde	2-Hydroxybenzylamine	474	475	Y	3.79	5.85
2	Glycine	3-(3,4-Dichlorophenoxy)benzaldehyde	2-Hydroxybenzylamine	547	548	Y	7.86	3.86
3	(S)-2,3-Diaminopropionic acid	3-(3,4-Dichlorophenoxy)benzaldehyde	2-Hydroxybenzylamine	590	591	Y	12.34	9.69
4	(S)-2,6-Diaminohexanoic acid	3-(3,4-Dichlorophenoxy)benzaldehyde	2-Hydroxybenzylamine	632	633	Y	1.72	3.78
5	Glycine	3-(4-Methoxyphenoxy)benzaldehyde	2-Hydroxybenzylamine	508	509	Y	6.16	3.41
6	(S)-2,3-Diaminopropionic acid	3-(4-Methoxyphenoxy)benzaldehyde	2-Hydroxybenzylamine	551	552	Y	3.17	1.36
7	(S)-2,6-Diaminohexanoic acid	3-(4-Methoxyphenoxy)benzaldehyde	2-Hydroxybenzylamine	593	594	Y	1.23	1.74
8	Glycine	3-Phenoxybenzaldehyde	2-Hydroxybenzylamine	478	479	Y	7.48	5.67
9	(S)-2,3-Diaminopropionic acid	3-Phenoxybenzaldehyde	2-Hydroxybenzylamine	521	522	Y	3.66	2.1
10	(S)-2,6-Diaminohexanoic acid	3-Phenoxybenzaldehyde	2-Hydroxybenzylamine	563	564	Y	0.85	0.26
11	Glycine	4-Phenoxybenzaldehyde	2-Hydroxybenzylamine	478	479	Y	10.47	7
12	(S)-2,3-Diaminopropionic acid	4-Phenoxybenzaldehyde	2-Hydroxybenzylamine	521	522	Y	5.44	2.62
13	(S)-2,6-Diaminohexanoic acid	4-Phenoxybenzaldehyde	2-Hydroxybenzylamine	563	564	Y	0.18	1.29
14	Glycine	4-Propoxybenzaldehyde	2-Hydroxybenzylamine	444	445	Y	8.31	5.36
15	(S)-2,3-Diaminopropionic acid	4-Propoxybenzaldehyde	2-Hydroxybenzylamine	487	488	Y	7.22	2.75
16	(S)-2,6-Diaminohexanoic acid	4-Propoxybenzaldehyde	2-Hydroxybenzylamine	529	530	Y	2.12	11.64
17	Glycine	3-Methoxy-4-hydroxy-5-bromobenzaldehyde	2-Hydroxybenzylamine	499	500	Y	15.6	35.08
18	(S)-2,3-Diaminopropionic acid	3-Methoxy-4-hydroxy-5-bromobenzaldehyde	2-Hydroxybenzylamine	542	543	Y	4.32	
19	(S)-2,6-Diaminohexanoic acid	3-Methoxy-4-hydroxy-5-bromobenzaldehyde	2-Hydroxybenzylamine	584	585	Y	26.5	
20	Glycine	9-Ethyl-3-carbazolecarboxaldehyde	2-Hydroxybenzylamine	503	504	Y	10.8	3.3
21	(S)-2,3-Diaminopropionic acid	9-Ethyl-3-carbazolecarboxaldehyde	2-Hydroxybenzylamine	547	548	Y	6.25	1.53
22	(S)-2,6-Diaminohexanoic acid	9-Ethyl-3-carbazolecarboxaldehyde	2-Hydroxybenzylamine	588	589	Y	2.12	1.79

TRG 2407								
		R8 = BOC						
				prod.	obs.(M+1)	>85%	MC-1	MC-4
Cpd #	R1	R2:Aldehyde	X: Amine	MW	M.W.	LCQ	IC50 M	IC50 M
1	L-Lysine	2,4-dichlorobenzaldehyde	Aniline	512	513	Y	5.57	10.65
2	L-Lysine	2,4-dichlorobenzaldehyde	N-methylaniline	526	527	Y	5.75	6.26
3	L-Lysine	2,4-dichlorobenzaldehyde	2-chloroaniline	546	547	Y	8.46	9.45
4	L-Lysine	2,4-dichlorobenzaldehyde	2-Methoxyaniline	542	543	Y	3.65	4.12
5	L-Lysine	2,4-dichlorobenzaldehyde	3-chloroaniline	546	547	Y	8.82	14.66
6	L-Lysine	2,4-dichlorobenzaldehyde	3-ethoxyaniline	556	557	Y	3.42	6.97
7	L-Lysine	2,4-dichlorobenzaldehyde	3-aminophenol	528	529	Y	4.38	no fit
8	L-Lysine	2,4-dichlorobenzaldehyde	4-chloroaniline	546	547	Y	10.88	21.23
9	L-Lysine	2,4-dichlorobenzaldehyde	4-Methoxyaniline	542	543	Y	2.53	6.22
10	L-Lysine	2,4-dichlorobenzaldehyde	Benzylamine	526	527	Y	4.13	3.85
11	L-Lysine	2,4-dichlorobenzaldehyde	N-benzylmethylamine	540	541	Y	5.31	6.17
12	L-Lysine	2,4-dichlorobenzaldehyde	2-chlorobenzylamine	560	561	Y	2.70	3.23
13	L-Lysine	2,4-dichlorobenzaldehyde	2-(trifluoromethyl)benzylamine	594	595	Y	8.50	9.25
14	L-Lysine	2,4-dichlorobenzaldehyde	2-Methoxybenzylamine	556	557	Y	0.37	0.41
15	L-Lysine	2,4-dichlorobenzaldehyde	2-ethoxybenzylamine	570	571	Y	1.20	0.78
16	L-Lysine	2,4-dichlorobenzaldehyde	3-methoxybenzylamine	556	557	Y	5.83	1.81
17	L-Lysine	2,4-dichlorobenzaldehyde	3-(trifluoromethyl)benzylamine	594	595	Y	10.07	9.22
18	L-Lysine	2,4-dichlorobenzaldehyde	4-Chlorobenzylamine	560	561	Y	3.31	2.83
19	L-Lysine	2,4-dichlorobenzaldehyde	4-methoxybenzylamine	556	557	Y	2.29	2.04
20	L-Lysine	2,4-dichlorobenzaldehyde	4-(trifluoromethyl)benzylamine	594	595	Y	3.78	3.49
21	L-Lysine	2,4-dichlorobenzaldehyde	phenethylamine	540	541	Y	1.03	0.36
22	L-Lysine	2,4-dichlorobenzaldehyde	2-chlorophenethylamine	574	575	Y	1.34	0.69
23	L-Lysine	2,4-dichlorobenzaldehyde	2-methoxyphenethylamine	570	571	Y	0.94	0.69
24	L-Lysine	2,4-dichlorobenzaldehyde	3-chlorophenethylamine	574	575	Y	1.79	0.80
25	L-Lysine	2,4-dichlorobenzaldehyde	4-methoxyphenthylamine	570	571	Y	1.47	0.62
26	L-Lysine	2,4-dichlorobenzaldehyde	3-phenyl-1-propylamine	554	555	Y	0.70	0.83
27	L-Lysine	2,4-dichlorobenzaldehyde	Cyclopentylamine	504	505	Y	0.57	0.53
28	L-Lysine	4-biphenylcarboxaldehyde	Isopropylamine	485	486	Y	0.31	3.60

29	L-Lysine	2,4-dichlorobenzaldehyde	Cycloheptylamine	532	533	Y	0.64	0.77
30	L-Lysine	2,4-dichlorobenzaldehyde	N-methylcyclohexylamine	532	533	Y	3.15	2.10
31	L-Lysine	2,4-dichlorobenzaldehyde	(aminomethyl)cyclohexane	532	533	Y	1.11	1.02
32	L-Lysine	2,4-dichlorobenzaldehyde	Piperidine	504	505	Y	3.29	2.14
33	L-Lysine	2,4-dichlorobenzaldehyde	Morpholine	506	507	Y	6.90	6.02
34*	L-Lysine	2,4-dichlorobenzaldehyde	1-aminopiperidine	519		N	3.97	2.01
35	L-Lysine	2,4-dichlorobenzaldehyde	Diethylamine	492	493	Y	6.52	3.41
36	L-Lysine	2,4-dichlorobenzaldehyde	Allylamine	476	477	Y	0.43	0.46

37	L-Lysine	2,4-dichlorobenzaldehyde	Isopropylamine	478	479	Y	0.91	0.54
38*	L-Lysine	2,4-dichlorobenzaldehyde	(2-Aminoethyl)-trimethylammonium	594		N	3.21	3.82
39	L-Lysine	2,4-dichlorobenzaldehyde	Ammonia	435	436	Y	0.91	0.11
40	L-Lysine	2,4-dichlorobenzaldehyde	none (OH)	436	437	Y	4.74	4.94
41	L-Lysine	4-acetamidobenzaldehyde	Aniline	486	487	Y	5.87	16.96
42	L-Lysine	4-acetamidobenzaldehyde	N-methylaniline	500	501	Y	4.23	7.90
43	L-Lysine	4-acetamidobenzaldehyde	2-chloroaniline	520	521	Y	7.07	11.20
44	L-Lysine	4-acetamidobenzaldehyde	2-Methoxyaniline	516	517	Y	1.15	10.38
45	L-Lysine	4-acetamidobenzaldehyde	3-chloroaniline	520	521	Y	7.91	10.95
46	L-Lysine	4-acetamidobenzaldehyde	3-ethoxyanilinc	530	531	Y	1.63	16.39
47	L-Lysine	4-acetamidobenzaldehyde	3-aminophenol	502	503	Y	0.84	no fit
48	L-Lysine	4-acetamidobenzaldehyde	4-chloroaniline	520	521	Y	4.48	10.81
49	L-Lysine	4-acetamidobenzaldehyde	4-Methoxyaniline	516	517	Y	2.36	no fit
50	L-Lysine	4-acetamidobenzaldehyde	Benzylamine	500	501	Y	0.35	9.10
51	L-Lysine	4-acetamidobenzaldehyde	N-benzylmethylamine	514	515	Y	2.16	13.49
52	L-Lysine	4-acetamidobenzaldehyde	2-chlorobenzylamine	534	535	Y	0.44	1.56
53	L-Lysine	4-acetamidobenzaldehyde	2-(trifluoromethyl)benzylamine	568	569	Y	1.27	0.79
54*	L-Lysine	4-biphenylcarboxaldehyde	(2-Aminoethyl)-trimethylammonium	601		N	4.23	14.82
55	L-Lysine	4-acetamidobenzaldehyde	2-ethoxybenzylamine	544	545	Y	0.19	14.89
56	L-Lysine	4-acetamidobenzaldehyde	3-methoxybenzylamine	530	531	Y	1.50	12.09
57	L-Lysine	4-acetamidobenzaldehyde	3-(trifluoromethyl)benzylamine	568	569	Y	2.46	3.65
58	L-Lysine	4-acetamidobenzaldehyde	4-Chlorobenzylamine	534	535	Y	0.54	2.78
59	L-Lysine	4-acetamidobenzaldehyde	4-methoxybenzylamine	530	531	Y	0.89	9.99
60	L-Lysine	4-acetamidobenzaldehyde	4-(trifluoromethyl)benzylamine	568	569	Y	0.77	3.32
61	L-Lysine	4-acetamidobenzaldehyde	Phenethylamine	514	515	Y	0.18	12.28
62	L-Lysine	4-acetamidobenzaldehyde	2-chlorophenethylamine	548	549	Y	0.23	4.22
63	L-Lysine	4-acetamidobenzaldehyde	2-methoxyphenethylamine	544	545	Y	0.28	10.08
64	L-Lysine	4-acetamidobenzaldehyde	3-chlorophenethylamine	548	549	Y	0.87	5.41
65	L-Lysine	4-acetamidobenzaldehyde	4-methoxyphenthylamine	544	545	Y	0.21	5.40
66	L-Lysine	4-acetamidobenzaldehyde	3-phenyl-1-propylamine	528	529	Y	0.23	3.29
67	L-Lysine	4-acetamidobenzaldehyde	Cyclopentylamine	478	479	Y	0.52	no fit
68	L-Lysine	4-biphenylcarboxaldehyde	Ammonia	443	444	Y	0.35	4.86

69	L-Lysine	4-acetamidobenzaldehyde	Cycloheptylamine	506	507	Y	0.29	15.30
70	L-Lysine	4-acetamidobenzaldehyde	N-methylcyclohexylamine	506	507	Y	1.02	43.56
71	L-Lysine	4-acetamidobenzaldehyde	(aminomethyl)cyclohexane	506	507	Y	0.64	13.50
72	L-Lysine	4-acetamidobenzaldehyde	Piperidine	478	479	Y	1.86	no fit
73	L-Lysine	4-acetamidobenzaldehyde	Morpholine	480	481	Y	10.55	no fit
74*	L-Lysine	4-acetamidobenzaldehyde	1-aminopiperidine	493		N	2.73	no fit
75	L-Lysine	4-acetamidobenzaldehyde	Diethylamine	466	467	Y	5.50	no fit
76*	L-Lysine	4-acetamidobenzaldehyde	Allylamine	450		N	0.51	no fit

77	L-Lysine	4-acetamidobenzaldehyde	Isopropylamine	452	453	Y	1.24	no fit
78*	L-Lysine	4-acetamidobenzaldehyde	(2-Aminoethyl)-trimethylammonium	568		N	4.60	no fit
79	L-Lysine	4-acetamidobenzaldehyde	Ammonia	410	411	Y	1.44	no fit
80	L-Lysine	4-acetamidobenzaldehyde	None	411	412	Y	11.60	no fit
81	L-Lysine	4-biphenylcarboxaldehyde	Aniline	519	520	Y	6.40	13.23
82	L-Lysine	4-biphenylcarboxaldehyde	N-methylaniline	533	534	Y	5.40	8.61
83	L-Lysine	4-biphenylcarboxaldehyde	2-chloroaniline	553	554	Y	7.02	9.53
84	L-Lysine	4-biphenylcarboxaldehyde	2-Methoxyaniline	549	550	Y	3.12	15.01
85	L-Lysine	4-biphenylcarboxaldehyde	3-chloroaniline	553	554	Y	7.09	12.47
86	L-Lysine	4-biphenylcarboxaldehyde	3-ethoxyaniline	563	564	Y	4.16	15.86
87	L-Lysine	4-biphenylcarboxaldehyde	3-aminophenol	535	536	Y	4.25	29.33
88	L-Lysine	4-biphenylcarboxaldehyde	4-chloroaniline	553	554	Y	8.24	12.47
89	L-Lysine	4-biphenylcarboxaldehyde	4-Methoxyaniline	549	550	Y	4.48	6.49
90	L-Lysine	4-biphenylcarboxaldehyde	Benzylamine	533	534	Y	3.43	5.45
91	L-Lysine	4-biphenylcarboxaldehyde	N-benzylmethylamine	547	548	Y	6.20	12.82
92	L-Lysine	4-biphenylcarboxaldehyde	2-chlorobenzylamine	567	568	Y	2.36	6.95
93	L-Lysine	4-biphenylcarboxaldehyde	2-(trifluoromethyl)benzylamine	601	602	Y	19.12	25.10
94	L-Lysine	4-biphenylcarboxaldehyde	2-Methoxybenzylamine	563	564	Y	0.82	5.88
95	L-Lysine	4-biphenylcarboxaldehyde	2-ethoxybenzylamine	577	578	Y	2.37	8.05
96	L-Lysine	4-biphenylcarboxaldehyde	3-methoxybenzylamine	563	564	Y	1.15	4.07
97	L-Lysine	4-biphenylcarboxaldehyde	3-(trifluoromethyl)benzylamine	601	602	Y	11.94	15.11
98	L-Lysine	4-biphenylcarboxaldehyde	4-Chlorobenzylamine	567	568	Y	3.04	6.27
99	L-Lysine	4-biphenylcarboxaldehyde	4-methoxybenzylamine	563	564	Y	3.24	9.05
100	L-Lysine	4-biphenylcarboxaldehyde	4-(trifluoromethyl)benzylamine	601	602	Y	2.76	6.49
101	L-Lysine	4-biphenylcarboxaldehyde	phenethylamine	547	548	Y	0.93	4.18
102	L-Lysine	4-biphenylcarboxaldehyde	2-chlorophenethylamine	581	582	Y	1.53	3.62
103	L-Lysine	4-biphenylcarboxaldehyde	2-methoxyphenethylamine	577	578	Y	1.72	9.61
104	L-Lysine	4-biphenylcarboxaldehyde	3-chlorophenethylamine	581	582	Y	3.98	7.74
105	L-Lysine	4-biphenylcarboxaldehyde	4-methoxyphenthylamine	577	578	Y	1.67	2.05
	L-Lysine	4-biphenylcarboxaldehyde	3-phenyl-1-propylamine	561	562	Y	2.21	4.53
107	L-Lysine	4-biphenylcarboxaldehyde	Cyclopentylamine	511	512	Y	0.92	5.56
108	L-Lysine	4-biphenylcarboxaldehyde	none	444	445	Y	3.54	10.78

109	L-Lysine	4-biphenylcarboxaldehyde	Cycloheptylamine	539	540	Y	1.19	5.36
110	L-Lysine	4-biphenylcarboxaldehyde	N-methylcyclohexylamine	539	540	Y	2.34	4.15
111	L-Lysine	4-biphenylcarboxaldehyde	(aminomethyl)cyclohexane	539	540	Y	1.43	4.57
112	L-Lysine	4-biphenylcarboxaldehyde	Piperidine	511	512	Y	1.66	6.99
113	L-Lysine	4-biphenylcarboxaldehyde	Morpholine	513	514	Y	5.57	10.34
114*	L-Lysine	4-biphenylcarboxaldehyde	1-aminopiperidine	526		N	3.04	10.00
115	L-Lysine	4-biphenylcarboxaldehyde	Diethylamine	499	500	Y	2.94	8.91
116	L-Lysine	4-biphenylcarboxaldehyde	Allylamine	483	484	Y	0.60	18.67

	TRG2408								
						obs.(M+1)	>85%	MC-1	MC-4
Cmpd #	R1: Amino Acids	R2: Aldehydes	R3: amines	R8:Substit. on R1 (C2-N)	M.W.	M.W.	LCQ	IC50 uM	IC50 uM
1	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	2-Methoxybenzylamine	Hydrogen	501	502	Y	0.51	15.06
2	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	2-Methoxybenzylamine	Phenylacetic acid	605	606	Y	1.18	8.55
3	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	2-Methoxybenzylamine	Glycine	544	545	Y	0.96	14.77
4	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	2-Methoxybenzylamine	Boc-Gly	558	559	Y	1.66	17.64
5	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	Hydrogen	477	478	Y	1.66	31.82
6	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	Phenylacetic acid	581	582	Y	0.61	7.16
7	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	Glycine	520	521	Y	1.30	44.54
8	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	Boc-Gly	534	535	Y	2.31	43.26
9	(S)-2,6-Diaminohexanoic acid	2,4-Dichlorobenzaldehyde	2-Methoxybenzylamine	Hydrogen	526	527	Y	1.81	2.17
10	(S)-2,6-Diaminohexanoic acid	2,4-Dichlorobenzaldehyde	2-Methoxybenzylamine	Phenylacetic acid	630	631	Y	4.34	10.94
11	(S)-2,6-Diaminohexanoic acid	2,4-Dichlorobenzaldehyde	2-Methoxybenzylamine	Glycine	569	570	Y	2.50	8.10
12	(S)-2,6-Diaminohexanoic acid	2,4-Dichlorobenzaldehyde	2-Methoxybenzylamine	Boc-Gly	583	584	Y	1.84	4.90
13	(S)-2,6-Diaminohexanoic acid	2,4-Dichlorobenzaldehyde	Cyclohexylamine	Hydrogen	502	503	Y	1.72	1.58
14	(S)-2,6-Diaminohexanoic acid	2,4-Dichlorobenzaldehyde	Cyclohexylamine	Phenylacetic acid	606	607	Y	2.11	5.52
15	(S)-2,6-Diaminohexanoic acid	2,4-Dichlorobenzaldehyde	Cyclohexylamine	Glycine	545	546	Y	0.76	6.30
16	(S)-2,6-Diaminohexanoic acid	2,4-Dichlorobenzaldehyde	Cyclohexylamine	Boc-Gly	559	560	Y	1.79	6.11
17	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	2-Methoxybenzylamine	Hydrogen	534	535	Y	2.34	15.05
18	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	2-Methoxybenzylamine	Phenylacetic acid	638	639	Y	4.06	12.48
19	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	2-Methoxybenzylamine	Glycine	577	578	Y	2.64	21.81
20	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	2-Methoxybenzylamine	Boc-Gly	591	592	Y	1.32	14.81
21	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Hydrogen	510	511	Y	1.73	17.39
22	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Phenylacetic acid	614	615	Y	2.77	11.44
23	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Glycine	553	554	Y	0.82	20.46

24	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Boc-Gly	567	568	Y	1.94	17.09
25	(R)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	2-Methoxybenzylamine	Boc	515	516	Y	1.02	38.03
26	(R)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	2-Methoxybenzylamine	Hydrogen	501	502	Y	1.14	38.91
27	(R)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	2-Methoxybenzylamine	Phenylacetic acid	605	606	Y	1.57	9.71
28	(R)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	2-Methoxybenzylamine	Glycine	544	545	Y	0.47	12.57
29	(R)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	2-Methoxybenzylamine	Boc-Gly	558	559	Y	0.68	21.83
30	(R)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	Boc	491	492	Y	1.17	45.56

31	(R)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	Hydrogen	477	478	Y	1.27	46.49
32	(R)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	Phenylacetic acid	581	582	Y	1.15	9.44
33	(R)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	Glycine	520	521	Y	1.06	38.66
34	(R)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	Boc-Gly	534	535	Y	2.14	33.62
35	(R)-2,6-Diaminohexanoic acid	2,4-Dichlorobenzaldehyde	2-Methoxybenzylamine	Boc	540	541	Y	2.77	4.89
36	(R)-2,6-Diaminohexanoic acid	2,4-Dichlorobenzaldehyde	2-Methoxybenzylamine	Hydrogen	526	527	Y	1.60	3.66
37	(R)-2,6-Diaminohexanoic acid	2,4-Dichlorobenzaldehyde	2-Methoxybenzylamine	Phenylacetic acid	630	631	Y	4.76	11.69
38	(R)-2,6-Diaminohexanoic acid	2,4-Dichlorobenzaldehyde	2-Methoxybenzylamine	Glycine	569	570	Y	1.70	5.57
39	(R)-2,6-Diaminohexanoic acid	2,4-Dichlorobenzaldehyde	2-Methoxybenzylamine	Boc-Gly	583	584	Y	1.80	6.05
40	(R)-2,6-Diaminohexanoic acid	2,4-Dichlorobenzaldehyde	Cyclohexylamine	Boc	516	517	Y	2.43	8.28
41	(R)-2,6-Diaminohexanoic acid	2,4-Dichlorobenzaldehyde	Cyclohexylamine	Hydrogen	502	503	Y	1.03	3.88
42	(R)-2,6-Diaminohexanoic acid	2,4-Dichlorobenzaldehyde	Cyclohexylamine	Phenylacetic acid	606	607	Y	1.93	4.24
43	(R)-2,6-Diaminohexanoic acid	2,4-Dichlorobenzaldehyde	Cyclohexylamine	Glycine	545	546	Y	1.63	7.49
44	(R)-2,6-Diaminohexanoic acid	2,4-Dichlorobenzaldehyde	Cyclohexylamine	Boc-Gly	559	560	Y	1.27	5.06
45	(R)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	2-Methoxybenzylamine	Boc	548	549	Y	1.55	15.19
46	(R)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	2-Methoxybenzylamine	Hydrogen	534	535	Y	1.85	20.35
47	(R)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	2-Methoxybenzylamine	Phenylacetic acid	638	639	Y	8.81	18.12
48	(R)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	2-Methoxybenzylamine	Glycine	577	578	Y	4.24	28.82
49	(R)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	2-Methoxybenzylamine	Boc-Gly	591	592	Y	1.70	19.03
50	(R)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Boc	524	525	Y	1.55	13.30
51	(R)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Hydrogen	510	511	Y	3.19	29.34
52	(R)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Phenylacetic acid	614	615	Y	3.69	12.29
53	(R)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Glycine	553	554	Y	1.00	14.78
54	(R)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Boc-Gly	567	568	Y	0.61	26.78
55	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	2-Methoxybenzylamine	Boc	501	502	Y	0.89	27.89
56	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	2-Methoxybenzylamine	Hydrogen	487	488	Y	0.71	38.21

57	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	2-Methoxybenzylamine	Phenylacetic acid	591	592	Y	0.28	6.02
58	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	2-Methoxybenzylamine	Glycine	530	531	Y	1.44	16.39
59	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	2-Methoxybenzylamine	Boc-Gly	544	545	Y	0.91	13.38
60	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	Boc	477	478	Y	0.69	20.70
61	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	Hydrogen	463	464	Y	0.69	35.18
62	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	Phenylacetic acid	567	568	Y	0.12	2.61
63	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	Glycine	506	507	Y	0.69	18.74
64	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	Boc-Gly	520	521	Y	2.67	24.97
65	(S)-2,5-Diaminopentanoic acid	2,4-Dichlorobenzaldehyde	2-Methoxybenzylamine	Boc	526	527	Y	2.07	4.36

66	(S)-2,5-Diaminopentanoic acid	2,4-Dichlorobenzaldehyde	2-Methoxybenzylamine	Hydrogen	512	513	Y	2.21	9.44
67	(S)-2,5-Diaminopentanoic acid	2,4-Dichlorobenzaldehyde	2-Methoxybenzylamine	Phenylacetic acid	616	617	Y	4.66	13.28
68	(S)-2,5-Diaminopentanoic acid	2,4-Dichlorobenzaldehyde	2-Methoxybenzylamine	Glycine	555	556	Y	1.66	4.51
69	(S)-2,5-Diaminopentanoic acid	2,4-Dichlorobenzaldehyde	2-Methoxybenzylamine	Boc-Gly	569	570	Y	1.66	3.88
70	(S)-2,5-Diaminopentanoic acid	2,4-Dichlorobenzaldehyde	Cyclohexylamine	Boc	502	503	Y	1.46	2.50
71	(S)-2,5-Diaminopentanoic acid	2,4-Dichlorobenzaldehyde	Cyclohexylamine	Hydrogen	488	489	Y	1.19	3.03
72	(S)-2,5-Diaminopentanoic acid	2,4-Dichlorobenzaldehyde	Cyclohexylamine	Phenylacetic acid	592	593	Y	1.94	5.87
73	(S)-2,5-Diaminopentanoic acid	2,4-Dichlorobenzaldehyde	Cyclohexylamine	Glycine	531	532	Y	1.08	4.05
74	(S)-2,5-Diaminopentanoic acid	2,4-Dichlorobenzaldehyde	Cyclohexylamine	Boc-Gly	545	546	Y	1.56	4.28
75	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	2-Methoxybenzylamine	Boc	534	535	Y	3.58	11.17
76	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	2-Methoxybenzylamine	Hydrogen	520	521	Y	2.54	12.51
77	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	2-Methoxybenzylamine	Phenylacetic acid	624	625	Y	8.22	27.59
78	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	2-Methoxybenzylamine	Glycine	563	564	Y	1.33	17.75
79	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	2-Methoxybenzylamine	Boc-Gly	577	578	Y	2.38	20.22
80	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Boc	510	511	Y	2.18	12.24
81	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Hydrogen	496	497	Y	4.41	18.03
82	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Phenylacetic acid	600	601	Y	10.19	16.44
83	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Glycine	539	540	Y	1.77	11.08
84	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Boc-Gly	553	554	Y	2.50	15.36
85	(S)-2,4-Diaminobutanoic acid	4-Acetamidobenzaldehyde	2-Methoxybenzylamine	Boc	487	488	Y	3.08	21.26
86	(S)-2,4-Diaminobutanoic acid	4-Acetamidobenzaldehyde	2-Methoxybenzylamine	Hydrogen	473	474	Y	3.31	15.94
87	(S)-2,4-Diaminobutanoic acid	4-Acetamidobenzaldehyde	2-Methoxybenzylamine	Phenylacetic acid	577	578	Y	3.27	7.07
88	(S)-2,4-Diaminobutanoic acid	4-Acetamidobenzaldehyde	2-Methoxybenzylamine	Glycine	516	517	Y	2.76	23.26
89	(S)-2,4-Diaminobutanoic acid	4-Acetamidobenzaldehyde	2-Methoxybenzylamine	Boc-Gly	530	531	Y	1.82	21.73
90	(S)-2,4-Diaminobutanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	Boc	463	464	Y	5.90	25.19
91	(S)-2,4-Diaminobutanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	Hydrogen	449	450	Y	9.94	28.06
92	(S)-2,4-Diaminobutanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	Phenylacetic acid	553	554	Y	4.51	1.54

93	(S)-2,4-Diaminobutanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	Glycine	492	493	Y	4.01	36.28
94	(S)-2,4-Diaminobutanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	Boc-Gly	506	507	Y	3.89	27.08
95	(S)-2,4-Diaminobutanoic acid	2,4-Dichlorobenzaldehyde	2-Methoxybenzylamine	Boc	512	513	Y	5.09	7.85
96	(S)-2,4-Diaminobutanoic acid	2,4-Dichlorobenzaldehyde	2-Methoxybenzylamine	Hydrogen	498	499	Y	6.33	8.72
97	(S)-2,4-Diaminobutanoic acid	2,4-Dichlorobenzaldehyde	2-Methoxybenzylamine	Phenylacetic acid	602	603	Y	9.06	6.90
98	(S)-2,4-Diaminobutanoic acid	2,4-Dichlorobenzaldehyde	2-Methoxybenzylamine	Glycine	541	542	Y	3.71	8.04
99	(S)-2,4-Diaminobutanoic acid	2,4-Dichlorobenzaldehyde	2-Methoxybenzylamine	Boc-Gly	555	556	Y	3.87	6.47
100	(S)-2,4-Diaminobutanoic acid	2,4-Dichlorobenzaldehyde	Cyclohexylamine	Boc	488	489	Y	6.98	6.10

101	(S)-2,4-Diaminobutanoic acid	2,4-Dichlorobenzaldehyde	Cyclohexylamine	Hydrogen	474	475	Y	7.89	5.68
102	(S)-2,4-Diaminobutanoic acid	2,4-Dichlorobenzaldehyde	Cyclohexylamine	Phenylacetic acid	578	579	Y	7.05	1.88
103	(S)-2,4-Diaminobutanoic acid	2,4-Dichlorobenzaldehyde	Cyclohexylamine	Glycine	517	518	Y	5.41	8.80
104	(S)-2,4-Diaminobutanoic acid	2,4-Dichlorobenzaldehyde	Cyclohexylamine	Boc-Gly	531	532	Y	5.65	9.06
105	(S)-2,4-Diaminobutanoic acid	4-Biphenylcarboxaldehyde	2-Methoxybenzylamine	Boc	520	521	Y	6.72	10.84
106	(S)-2,4-Diaminobutanoic acid	4-Biphenylcarboxaldehyde	2-Methoxybenzylamine	Hydrogen	506	507	Y	6.70	14.92
107	(S)-2,4-Diaminobutanoic acid	4-Biphenylcarboxaldehyde	2-Methoxybenzylamine	Phenylacetic acid	610	611	Y	14.68	16.40
108	(S)-2,4-Diaminobutanoic acid	4-Biphenylcarboxaldehyde	2-Methoxybenzylamine	Glycine	549	550	Y	4.61	17.54
109	(S)-2,4-Diaminobutanoic acid	4-Biphenylcarboxaldehyde	2-Methoxybenzylamine	Boc-Gly	563	564	Y	4.75	9.73
110	(S)-2,4-Diaminobutanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Boc	496	497	Y	5.37	9.01
111	(S)-2,4-Diaminobutanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Hydrogen	482	483	Y	7.52	12.02
112	(S)-2,4-Diaminobutanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Phenylacetic acid	586	587	Y	8.79	10.36
113	(S)-2,4-Diaminobutanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Glycine	525	526	Y	3.78	12.67
114	(S)-2,4-Diaminobutanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Boc-Gly	539	540	Y	3.24	10.52

	TRG 2409								
		R8 = BOC						MC-1	MC-4
						obs.(M+1)	>85%	AVERAGE	AVERAGE
Cpd #	R1: Amino Acids	R2: Aldehydes	X: amines	R5: Substit. on R2 NH2	M.W.	M.W.	LCQ	IC50	IC50
1	(S)-2,6-Diaminohexanoic acid	4-nitrobenzaldehyde	2-Methoxybenzylamine	Benzoic acid	577	578	Y	0.54	10.47
2	(S)-2,6-Diaminohexanoic acid	4-nitrobenzaldehyde	2-Methoxybenzylamine	Butyric acid	543	544	Y	0.22	10.69
3	(S)-2,6-Diaminohexanoic acid	4-nitrobenzaldehyde	2-Methoxybenzylamine	Cyclohexane carboxylic acid	583	584	Y	2.47	15.28
4	(S)-2,6-Diaminohexanoic acid	4-nitrobenzaldehyde	2-Methoxybenzylamine	Isobutyric acid	543	544	Y	0.68	15.82
5	(S)-2,6-Diaminohexanoic acid	4-nitrobenzaldehyde	2-Methoxybenzylamine	Methoxyacetic acid	545	546	Y	1.15	18.35
6	(S)-2,6-Diaminohexanoic acid	4-nitrobenzaldehyde	2-Methoxybenzylamine	p-anisic acid	607	608	Y	4.00	13.37
7	(S)-2,6-Diaminohexanoic acid	4-nitrobenzaldehyde	2-Methoxybenzylamine	Phenylacetic acid	591	592	Y	1.03	9.81
8	(S)-2,6-Diaminohexanoic acid	4-nitrobenzaldehyde	2-Methoxybenzylamine	Propionic acid	529	530	Y	0.64	12.59
9	(S)-2,6-Diaminohexanoic acid	4-nitrobenzaldehyde	2-Methoxybenzylamine	4-Methoxyphenylacetic acid	621	622	Y	1.70	20.99
10	(S)-2,6-Diaminohexanoic acid	4-nitrobenzaldehyde	2-Methoxybenzylamine	2-Norbornaneacetic acid	609	610	Y	2.60	20.72
11	(S)-2,6-Diaminohexanoic acid	4-nitrobenzaldehyde	2-Methoxybenzylamine	3,4-Dichlorophenylacetic acid	660	661	Y	9.82	49.83
12	(S)-2,6-Diaminohexanoic acid	4-nitrobenzaldehyde	2-Methoxybenzylamine	4-Chlorobenzoic acid	611	612	Y	5.04	22.86
13	(S)-2,6-Diaminohexanoic acid	4-nitrobenzaldehyde	Cyclohexylamine	Benzoic acid	553	554	Y	1.46	17.41
14	(S)-2,6-Diaminohexanoic acid	4-nitrobenzaldehyde	Cyclohexylamine	Butyric acid	519	520	Y	0.10	15.09
15	(S)-2,6-Diaminohexanoic acid	4-nitrobenzaldehyde	Cyclohexylamine	Cyclohexane carboxylic acid	559	560	Y	1.65	16.22
16	(S)-2,6-Diaminohexanoic acid	4-nitrobenzaldehyde	Cyclohexylamine	Isobutyric acid	519	520	Y	0.95	20.96
17	(S)-2,6-Diaminohexanoic acid	4-nitrobenzaldehyde	Cyclohexylamine	Methoxyacetic acid	521	522	Y	2.72	27.50
18	(S)-2,6-Diaminohexanoic acid	4-nitrobenzaldehyde	Cyclohexylamine	p-anisic acid	583	584	Y	7.51	16.88
19	(S)-2,6-Diaminohexanoic acid	4-nitrobenzaldehyde	Cyclohexylamine	Phenylacetic acid	567	568	Y	2.08	15.50
20	(S)-2,6-Diaminohexanoic acid	4-nitrobenzaldehyde	Cyclohexylamine	Propionic acid	505	506	Y	0.88	19.80
21	(S)-2,6-Diaminohexanoic acid	4-nitrobenzaldehyde	Cyclohexylamine	4-Methoxyphenylacetic acid	597	598	Y	2.63	14.70
22	(S)-2,6-Diaminohexanoic acid	4-nitrobenzaldehyde	Cyclohexylamine	2-Norbornaneacetic acid	585	586	Y	1.53	12.32

23	(S)-2,6-Diaminohexanoic acid	4-nitrobenzaldehyde	Cyclohexylamine	3,4-Dichlorophenylacetic acid	636	637	Y	4.77	19.59
24	(S)-2,6-Diaminohexanoic acid	4-nitrobenzaldehyde	Cyclohexylamine	4-Chlorobenzoic acid	587	588	Y	3.95	12.15

221	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Ammonia	Phenylacetic acid	513	514	Y	0.08	0.85
222	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Ammonia	4-Bromophenylacetic acid	591	592	Y	0.12	
223	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Ammonia	4-Methoxyphenylacetic acid	543	544	Y	0.10	0.63
224	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Ammonia	Benzoic acid	499	500	Y	0.12	1.32
225	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Ammonia	4-Chlorobenzoic acid	533	534	Y	0.12	1.12
226	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Ammonia	4-Methoxybenzoic acid	529	530	Y	0.10	
227	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Ammonia	2-Naphthylacetic acid	563	564	Y	0.17	
228	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Ammonia	Cyclohexylacetic acid	519	520	Y		
229	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Ammonia	Glycine	452	453	Y	0.23	

	TRG 2411								
						obs.(M+1)	>85%	MC-1	MC-4
Cpd #	R1: Amino Acid	R2: Aldehyde	R3: amine	R3: Substit. on R1 a-NH2	M.W.	M.W.	LCQ	IC50 u	IC50 u
1	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Phenethylamine	Hydrogen	532	533	Y	0.60	1.22
2	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Phenethylamine	Acetic acid	560	561	Y	0.55	
3	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Phenethylamine	Phenylacetic acid	636	637	Y	0.88	
4	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Phenethylamine	Boc-Gly	589	590	Y	0.70	
5	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Phenethylamine	Gly	575	576	Y	0.79	
6	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Phenethylamine	Boc-Ala	603	604	Y	0.47	
7	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Phenethylamine	Hydroxy Acetic acid	576	577	Y	0.63	
8	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Phenethylamine	Boc-Phe	679	680	Y	0.76	
9	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Phenethylamine	Succinic anhydride	586	646	Y	0.13	1.27
10	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Phenethylamine	Methoxyacetic acid	590	591	Y	1.10	
11	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Phenethylamine	Butyric acid	588	589	Y	0.83	1.80
12	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Phenethylamine	Cyclohexanecarboxylic acid	628	629	Y	0.73	
13	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Phenethylamine	Benzoic acid	622	623	Y	1.36	
14	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Acetic acid	538	539	Y	0.46	
15	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Boc-Ala	581	582	Y	0.73	
16	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Hydroxy Acetic acid	554	555	Y	0.90	
17	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Boc-Phe	657	658	Y	0.39	
18	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Succinic anhydride	564	624	Y	0.08	
19	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Methoxyacetic acid	568	569	Y	0.49	
20	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Butyric acid	566	567	Y	0.61	0.77
21	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Cyclohexanecarboxylic acid	606	607	Y	0.27	1.01
22	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Benzoic acid	600	601	Y	0.42	1.73
23	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Ammonia	Hydrogen	428	429	Y	0.59	
24	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Ammonia	Acetic acid	456	457	Y	0.53	
25	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Ammonia	Phenylacetic acid	532	533	Y	0.35	
26	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Ammonia	Boc-Gly	485	486	Y	0.09	6.17
27	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Ammonia	Gly	471	472	Y	0.66	

28	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Ammonia	Boc-Ala	499	500	Y	0.56	1.23
29	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Ammonia	Hydroxy Acetic acid	472	473	Y	0.30	1.42
30	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Ammonia	Boc-Phe	575	576	Y	0.30	1.33
31	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Ammonia	Succinic anhydride	482	542	Y	0.97	
32	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Ammonia	Methoxyacetic acid	486	487	Y	0.55	
33	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Ammonia	Butyric acid	484	485	Y	0.39	1.73
34	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Ammonia	Cyclohexanecarboxylic acid	524	525	Y	0.35	
35	(S)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Ammonia	Benzoic acid	518	519	Y	0.51	
36	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Phenethylamine	Hydrogen	499	500	Y	0.13	
37	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Phenethylamine	Acetic acid	527	528	Y	0.13	
38	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Phenethylamine	Butyric acid	555	556	Y	0.09	1.33
39	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Phenethylamine	Succinic anhydride	553	59	Y	0.03	
40	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Phenethylamine	Phenylacetic acid	603	604	Y	0.19	1.00

41	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Phenethylamine	4-Bromophenylacetic acid	681	682	Y	0.49	1.64
42	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Phenethylamine	4-Methoxyphenylacetic acid	633	634	Y	0.32	1.56
43	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Phenethylamine	Benzoic acid	589	590	Y	0.19	1.03
44	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Phenethylamine	4-Chlorobenzoic acid	623	624	Y	0.16	1.04
45	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Phenethylamine	4-Methoxybenzoic acid	619	620	Y	0.12	0.84
46	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Phenethylamine	2-Naphthylacetic acid	653	654	Y	0.89	1.33
47	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Phenethylamine	Cyclohexylacetic acid	609	610	Y	0.22	
48	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Phenethylamine	Glycine	542	543	Y	0.30	
49	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	Acetic acid	505	506	Y	0.22	
50	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	Butyric acid	533	534	Y	0.08	
51	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	Succinic anhydride	531	591	Y		
52	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	4-Bromophenylacetic acid	659	660	Y	0.55	0.86
53	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	4-Methoxyphenylacetic acid	611	612	Y	0.28	1.65
54	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	Benzoic acid	567	568	Y	0.13	1.79
55	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	4-Chlorobenzoic acid	601	602	Y	0.09	2.05
56	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	4-Methoxybenzoic acid	597	598	Y	0.13	
57	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	2-Naphthylacetic acid	631	632	Y	0.92	1.19
58	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	Cyclohexylacetic acid	587	588	Y	0.22	1.11
59	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Ammonia	Hydrogen	395	396	Y	0.37	
60	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Ammonia	Acetic acid	423	424	Y	0.05	
61	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Ammonia	Butyric acid	451	452	Y	0.11	
62	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Ammonia	Succinic anhydride	449	509	Y		
63	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Ammonia	Phenylacetic acid	499	500	Y	0.24	1.82
64	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Ammonia	4-Bromophenylacetic acid	577	578	Y	0.48	
65	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Ammonia	4-Methoxyphenylacetic acid	529	530	Y	0.39	
66	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Ammonia	Benzoic acid	485	486	Y	0.11	
67	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Ammonia	4-Chlorobenzoic acid	519	520	Y	0.21	
68	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Ammonia	4-Methoxybenzoic acid	515	516	Y	0.12	
69	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Ammonia	2-Naphthylacetic acid	549	550	Y	0.37	
70	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Ammonia	Cyclohexylacetic acid	505	506	Y	0.16	
71	(S)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Ammonia	Glycine	438	439	Y	0.39	

72	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Phenethylamine	Hydrogen	527	528	Y	0.25	
73	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Phenethylamine	Boc	541	542	Y	0.19	
74	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Phenethylamine	Acetic acid	555	556	Y	0.11	2.24
75	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Phenethylamine	Butyric acid	583	584	Y	0.13	1.05
76	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Phenethylamine	Succinic anhydride	581	641	Y		
77	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Phenethylamine	Phenylacetic acid	631	632	Y	0.22	1.49
78	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Phenethylamine	4-Bromophenylacetic acid	709	710	Y	0.45	1.32
79	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Phenethylamine	4-Methoxyphenylacetic acid	661	662	Y	0.37	
80	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Phenethylamine	Benzoic acid	617	618	Y	0.17	1.83
81	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Phenethylamine	4-Chlorobenzoic acid	651	652	Y	0.18	1.38
82	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Phenethylamine	4-Methoxybenzoic acid	647	648	Y	0.29	1.46
83	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Phenethylamine	2-Naphthylacetic acid	681	682	Y	0.57	1.06
84	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Phenethylamine	Cyclohexylacetic acid	637	638	Y	0.22	0.76
85	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Phenethylamine	Glycine	570	571	Y	0.31	

86	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Cyclohexylamine	Hydrogen	505	506	Y		
87	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Cyclohexylamine	Acetic acid	533	534	Y	0.23	0.83
88	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Cyclohexylamine	Butyric acid	561	562	Y	0.24	1.50
89	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Cyclohexylamine	Succinic anhydride	559	619	Y	0.06	
90	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Cyclohexylamine	Phenylacetic acid	609	610	Y	0.25	1.17
91	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Cyclohexylamine	4-Bromophenylacetic acid	687	688	Y	0.64	
92	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Cyclohexylamine	4-Methoxyphenylacetic acid	639	640	Y	0.30	
93	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Cyclohexylamine	Benzoic acid	595	596	Y	0.13	
94	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Cyclohexylamine	4-Chlorobenzoic acid	629	630	Y	0.09	1.71
95	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Cyclohexylamine	4-Methoxybenzoic acid	625	626	Y	0.11	1.03
96	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Cyclohexylamine	2-Naphthylacetic acid	659	660	Y	0.60	1.65
97	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Cyclohexylamine	Cyclohexylacetic acid	615	616	Y		
98	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Cyclohexylamine	Glycine	548	549	Y		
99	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Ammonia	Hydrogen	423	424	Y	0.27	
100	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Ammonia	Boc	437	438	Y	0.13	
101	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Ammonia	Acetic acid	451	452	Y	0.10	
102	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Ammonia	Butyric acid	479	480	Y	0.09	1.17
103	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Ammonia	Succinic anhydride	477	537	Y	0.02	
104	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Ammonia	Phenylacetic acid	527	528	Y	0.16	0.59
105	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Ammonia	4-Bromophenylacetic acid	605	606	Y	0.21	0.91
106	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Ammonia	4-Methoxyphenylacetic acid	557	558	Y	0.37	
107	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Ammonia	Benzoic acid	513	514	Y	0.34	
108	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Ammonia	4-Chlorobenzoic acid	547	548	Y	0.16	
109	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Ammonia	4-Methoxybenzoic acid	543	544	Y	0.10	1.40
110	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Ammonia	2-Naphthylacetic acid	577	578	Y	0.10	1.05
111	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Ammonia	Cyclohexylacetic acid	533	534	Y	0.04	1.47
112	(S)-2,6-Diaminohexanoic acid	4-Butyramidobenzaldehyde	Ammonia	Glycine	466	467	Y	0.20	1.45
113	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Phenethylamine	Hydrogen	518	519	Y	0.50	
114	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Phenethylamine	Boc	532	533	Y	0.76	
115	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Phenethylamine	Acetic acid	546	547	Y	0.82	1.43
116	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Phenethylamine	Phenylacetic acid	622	623	Y	1.24	1.98

117	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Phenethylamine	Boc-Gly	575	576	Y	0.97	
118	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Phenethylamine	Gly	561	562	Y	0.35	
119	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Phenethylamine	Boc-Ala	589	590	Y	0.37	
120	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Phenethylamine	Hydroxy Acetic acid	562	563	Y	1.70	
121	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Phenethylamine	Boc-Phe	665	666	Y	1.07	
122	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Phenethylamine	Succinic anhydride	572	632	Y	0.15	
123	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Phenethylamine	Methoxyacetic acid	576	577	Y	1.54	
124	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Phenethylamine	Butyric acid	574	575	Y	1.54	
125	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Phenethylamine	Cyclohexanecarboxylic acid	614	615	Y	0.82	
126	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Phenethylamine	Benzoic acid	608	609	Y	1.32	1.49
127	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Acetic acid	524	525	Y	1.48	
128	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Boc-Ala	567	568	Y	1.57	
129	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Hydroxy Acetic acid	540	541	Y		
130	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Boc-Phe	643	644	Y	0.92	

131	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Succinic anhydride	550	610	Y	0.23	
132	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Methoxyacetic acid	554	555	Y		
133	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Butyric acid	552	553	Y	1.46	1.59
134	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Cyclohexanecarboxylic acid	592	593	Y	1.48	
135	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Cyclohexylamine	Benzoic acid	586	587	Y	1.98	
136	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Ammonia	Hydrogen	414	415	Y	1.73	
137	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Ammonia	Boc	428	429	Y	1.62	
138	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Ammonia	Acetic acid	442	443	Y	1.27	
139	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Ammonia	Phenylacetic acid	518	519	Y	1.46	
140	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Ammonia	Boc-Gly	471	472	Y	1.36	
141	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Ammonia	Gly	457	458	Y	1.15	
142	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Ammonia	Boc-Ala	485	486	Y	1.28	
143	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Ammonia	Hydroxy Acetic acid	458	459	Y		
144	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Ammonia	Boc-Phe	561	562	Y	1.22	
145	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Ammonia	Succinic anhydride	468	528	Y	0.11	
146	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Ammonia	Methoxyacetic acid	472	473	Y	1.22	1.46
147	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Ammonia	Butyric acid	470	471	N	1.26	1.19
148	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Ammonia	Cyclohexanecarboxylic acid	510	511	N	0.96	1.96
149	(S)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Ammonia	Benzoic acid	504	505	N	1.17	0.49
150	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Phenethylamine	Hydrogen	485	486	Y	0.12	4.54
151	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Phenethylamine	Boc	499	500	Y	0.09	1.78
152	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Phenethylamine	Acetic acid	513	514	Y	0.06	0.52
153	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Phenethylamine	Butyric acid	541	542	Y	0.08	0.59
154	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Phenethylamine	Succinic anhydride	539	599	Y	0.01	2.30
155	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Phenethylamine	Phenylacetic acid	589	590	Y	0.09	0.72
156	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Phenethylamine	4-Bromophenylacetic acid	667	668	Y	0.12	0.66
157	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Phenethylamine	4-Methoxyphenylacetic acid	619	620	Y	0.11	0.67
158	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Phenethylamine	Benzoic acid	575	576	Y	0.10	0.41
159	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Phenethylamine	4-Chlorobenzoic acid	609	610	Y	0.10	0.35
160	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Phenethylamine	4-Methoxybenzoic acid	605	606	Y	0.09	0.51
161	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Phenethylamine	2-Naphthylacetic acid	639	640	Y	0.16	0.64

162	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Phenethylamine	Cyclohexylacetic acid	595	596	Y	0.11	1.22
163	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Phenethylamine	Glycine	528	529	Y	0.22	
164	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	Acetic acid	491	492	Y	0.18	4.02
165	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	Butyric acid	519	520	Y	0.09	
166	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	Succinic anhydride	517	577	Y	0.04	
167	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	4-Bromophenylacetic acid	645	646	Y	0.37	1.11
168	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	4-Methoxyphenylacetic acid	597	598	Y	0.23	
169	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	Benzoic acid	553	554	Y	0.22	0.44
170	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	4-Chlorobenzoic acid	587	588	Y	0.13	
171	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	4-Methoxybenzoic acid	583	584	Y	0.15	
172	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	2-Naphthylacetic acid	617	618	Y	0.22	
173	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	Cyclohexylacetic acid	573	574	Y	0.14	1.59
174	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Ammonia	Hydrogen	381	382	Y	0.48	
175	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Ammonia	Boc	395	396	Y	0.29	

176	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Ammonia	Acetic acid	409	410	Y	0.22	
177	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Ammonia	Butyric acid	437	438	Y	0.11	
178	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Ammonia	Succinic anhydride	435	495	Y	0.02	
179	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Ammonia	Phenylacetic acid	485	486	Y	0.07	1.43
180	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Ammonia	4-Bromophenylacetic acid	563	564	Y	0.12	1.06
181	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Ammonia	4-Methoxyphenylacetic acid	515	516	Y	0.11	
182	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Ammonia	Benzoic acid	471	472	Y	0.20	
183	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Ammonia	4-Chlorobenzoic acid	505	506	Y	0.13	
184	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Ammonia	4-Methoxybenzoic acid	501	502	Y	0.09	1.61
185	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Ammonia	2-Naphthylacetic acid	535	536	Y	0.10	
186	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Ammonia	Cyclohexylacetic acid	491	492	Y	0.03	0.58
187	(S)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Ammonia	Glycine	424	425	Y	0.06	
188	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Phenethylamine	Hydrogen	513	514	Y	0.13	
189	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Phenethylamine	Boc	527	528	Y	0.12	
190	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Phenethylamine	Acetic acid	541	542	Y	0.19	0.21
191	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Phenethylamine	Butyric acid	569	570	Y	0.12	0.52
192	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Phenethylamine	Succinic anhydride	567	627	Y	0.07	0.88
193	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Phenethylamine	Phenylacetic acid	617	618	Y	0.15	1.24
194	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Phenethylamine	4-Bromophenylacetic acid	695	696	Y	0.24	1.36
195	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Phenethylamine	4-Methoxyphenylacetic acid	647	648	Y	0.16	1.44
196	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Phenethylamine	Benzoic acid	603	604	Y	0.12	1.05
197	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Phenethylamine	4-Chlorobenzoic acid	637	638	Y	0.08	
198	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Phenethylamine	4-Methoxybenzoic acid	633	634	Y	0.12	
199	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Phenethylamine	2-Naphthylacetic acid	667	668	Y	0.17	
200	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Phenethylamine	Cyclohexylacetic acid	623	624	Y	0.13	1.34
201	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Phenethylamine	Glycine	556	557	Y	0.30	
202	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Cyclohexylamine	Hydrogen	491	492	Y	0.22	
203	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Cyclohexylamine	Boc	505	506	Y	0.17	
204	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Cyclohexylamine	Acetic acid	519	520	Y	0.15	
205	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Cyclohexylamine	Butyric acid	547	548	Y	0.25	
206	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Cyclohexylamine	Succinic anhydride	545	605	Y	0.07	

207	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Cyclohexylamine	Phenylacetic acid	595	596	Y	0.19	
208	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Cyclohexylamine	4-Bromophenylacetic acid	673	674	Y	0.47	0.86
209	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Cyclohexylamine	4-Methoxyphenylacetic acid	625	626	Y	0.35	1.33
210	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Cyclohexylamine	Benzoic acid	581	582	Y	0.30	
211	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Cyclohexylamine	4-Chlorobenzoic acid	615	616	Y	0.10	
212	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Cyclohexylamine	4-Methoxybenzoic acid	611	612	Y	0.10	1.93
213	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Cyclohexylamine	2-Naphthylacetic acid	645	646	Y	0.22	1.95
214	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Cyclohexylamine	Cyclohexylacetic acid	601	602	Y	0.08	
215	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Cyclohexylamine	Glycine	534	535	Y	0.38	
216	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Ammonia	Hydrogen	409	410	Y	0.11	
217	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Ammonia	Boc	423	424	Y	0.09	
218	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Ammonia	Acetic acid	437	438	Y	0.07	9.59
219	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Ammonia	Butyric acid	465	466	Y	0.10	2.97
220	(S)-2,5-Diaminopentanoic acid	4-Butyramidobenzaldehyde	Ammonia	Succinic anhydride	463	523	Y	0.02	

	TRG 2412								
						obs.(M+1)	>85%	MC-1	MC-4
Cpd #	R1: Amino Acid	R2: Aldehyde	R3amine	R8: Substit. on R1 a-NH2	M.W.	M.W.	LCQ	IC50 uM	IC50 uM
1	(S)-2,6-Diaminohexanoic acid	4-Valeramidobenzaldehyde	Phenethylamine	Boc	555	556	Y	0.38	
2	(S)-2,6-Diaminohexanoic acid	4-Valeramidobenzaldehyde	Phenethylamine	Phenylacetic acid	645	646	Y	0.47	
3	(S)-2,6-Diaminohexanoic acid	4-Valeramidobenzaldehyde	Phenethylamine	Benzoic acid	631	632	Y	0.36	
4	(S)-2,6-Diaminohexanoic acid	4-Ethoxybenzaldehyde	Phenethylamine	Boc	514	515	Y	0.31	0.32
5	(S)-2,6-Diaminohexanoic acid	4-Ethoxybenzaldehyde	Phenethylamine	Phenylacetic acid	604	605	Y	0.49	
6	(S)-2,6-Diaminohexanoic acid	4-Ethoxybenzaldehyde	Phenethylamine	Benzoic acid	590	591	Y	0.59	
7	(S)-2,6-Diaminohexanoic acid	4-Propoxybenzaldehyde	Phenethylamine	Boc	528	529	Y	0.42	
8	(S)-2,6-Diaminohexanoic acid	4-Propoxybenzaldehyde	Phenethylamine	Phenylacetic acid	618	619	Y	0.83	
9	(S)-2,6-Diaminohexanoic acid	4-Propoxybenzaldehyde	Phenethylamine	Benzoic acid	604	605	Y	0.57	
10	(S)-2,6-Diaminohexanoic acid	4-Butoxybenzaldehyde	Phenethylamine	Boc	542	543	Y	0.31	
11	(S)-2,6-Diaminohexanoic acid	4-Butoxybenzaldehyde	Phenethylamine	Phenylacetic acid	632	633	Y	0.82	
12	(S)-2,6-Diaminohexanoic acid	4-Butoxybenzaldehyde	Phenethylamine	Benzoic acid	618	619	Y	0.54	
13	(S)-2,6-Diaminohexanoic acid	4-Amylbenzaldehyde	Phenethylamine	Boc	540	541	Y	0.45	
14	(S)-2,6-Diaminohexanoic acid	4-Amylbenzaldehyde	Phenethylamine	Phenylacetic acid	630	631	Y	0.88	
15	(S)-2,6-Diaminohexanoic acid	4-Amylbenzaldehyde	Phenethylamine	Benzoic acid	618	619	Y	0.75	
16	(S)-2,5-Diaminopentanoic acid	4-Valeramidobenzaldehyde	Phenethylamine	Boc	541	542	Y	0.09	1.48
17	(S)-2,5-Diaminopentanoic acid	4-Valeramidobenzaldehyde	Phenethylamine	Phenylacetic acid	631	632	Y	0.27	1.15
18	(S)-2,5-Diaminopentanoic acid	4-Valeramidobenzaldehyde	Phenethylamine	Benzoic acid	617	618	Y	0.19	
19	(S)-2,5-Diaminopentanoic acid	4-Ethoxybenzaldehyde	Phenethylamine	Boc	500	501	Y	0.16	
20	(S)-2,5-Diaminopentanoic acid	4-Ethoxybenzaldehyde	Phenethylamine	Phenylacetic acid	590	591	Y	0.15	
21	(S)-2,5-Diaminopentanoic acid	4-Ethoxybenzaldehyde	Phenethylamine	Benzoic acid	576	577	Y	0.17	0.23
22	(S)-2,5-Diaminopentanoic acid	4-Propoxybenzaldehyde	Phenethylamine	Boc	514	515	Y	0.20	
23	(S)-2,5-Diaminopentanoic acid	4-Propoxybenzaldehyde	Phenethylamine	Phenylacetic acid	604	605	Y	0.35	
24	(S)-2,5-Diaminopentanoic acid	4-Propoxybenzaldehyde	Phenethylamine	Benzoic acid	590	591	Y	0.41	
25	(S)-2,5-Diaminopentanoic acid	4-Butoxybenzaldehyde	Phenethylamine	Boc	528	529	Y	0.16	1.06
26	(S)-2,5-Diaminopentanoic acid	4-Butoxybenzaldehyde	Phenethylamine	Phenylacetic acid	618	619	Y	0.20	
27	(S)-2,5-Diaminopentanoic acid	4-Butoxybenzaldehyde	Phenethylamine	Benzoic acid	604	605	Y	0.25	

28	(S)-2,5-Diaminopentanoic acid	4-Amylbenzaldehyde	Phenethylamine	Boc	526	527	Y	0.27	
29	(S)-2,5-Diaminopentanoic acid	4-Amylbenzaldehyde	Phenethylamine	Phenylacetic acid	616	617	Y	0.50	
30	(S)-2,5-Diaminopentanoic acid	4-Amylbenzaldehyde	Phenethylamine	Benzoic acid	602	603	Y	0.62	1.06

	TRG2413					obs.(M+1)	>85%	MC-1	MC-4
Cpd #	R1: Amino Acid	R2: Aldehyde	X: amine	R8: Subst., R1 a-NH2	M.W.	M.W.	LCQ	IC50 uM	IC50 uM
1	(R)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Phenethylamine	Boc-Gly	589	590	Y	0.441	
2	(R)-2,6-Diaminohexanoic acid	4-Biphenylcarboxaldehyde	Ammonia	Boc-Gly	485	486	Y	0.538	
3	(R)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Ammonia	Boc-Gly	452	453	Y	1.556	
4	(R)-2,6-Diaminohexanoic acid	4-Acetamidobenzaldehyde	Phenethylamine	Boc-Gly	556	557	Y	0.341	
5	(R)-2,6-Diaminohexanoic acid	4-Nitrobenzaldehyde	Phenethylamine	Boc	515	516	Y	4.885	
6	(R)-2,6-Diaminohexanoic acid	4-Nitrobenzaldehyde	Ammonia	Boc	412	413	Y	6.509	
7	(R)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Ammonia	Gly	457	458	Y	1.537	
8	(R)-2,5-Diaminopentanoic acid	4-Biphenylcarboxaldehyde	Ammonia	Boc	428	429	Y	1.835	
9	(R)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Phenethylamine	Phenylacetic acid	589	590	Y	0.263	1.339
10	(R)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Cyclohexylamine	Phenylacetic acid	567	568	Y	0.307	
11	(R)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Ammonia	Phenylacetic acid	485	486	Y	0.125	
12	(R)-2,5-Diaminopentanoic acid	4-Acetamidobenzaldehyde	Phenethylamine	Boc	499	500	Y	0.187	
13	(R)-2,5-Diaminopentanoic acid	4-Nitrobenzaldehyde	Phenethylamine	Phenylacetic acid	591	592	Y	1.067	
14	(R)-2,5-Diaminopentanoic acid	4-Nitrobenzaldehyde	Cyclohexylamine	Phenylacetic acid	569	570	Y	1.569	
15	(R)-2,5-Diaminopentanoic acid	4-Nitrobenzaldehyde	Ammonia	Phenylacetic acid	487	488	Y	1.917	
16	(R)-2,5-Diaminopentanoic acid	4-Nitrobenzaldehyde	Phenethylamine	Boc	501	502	Y	1.270	0.401

	TRG 2414							
R1 = (S)-2,6-Diaminohexanoic acid		IBP = 4-isobutyl-α-methylphenyl acetic acid						
					obs.(M+1)	>85%	MC-1	MC-4
Cmpd #	**R2: Aldehydes**	**X: amines**	**R8: acids**	**M.W.**	**M.W.**	**LCQ**	**IC50 μM**	**IC50 μM**
1	2,4-Dichlorobenzaldehyde	2-(trifluoromethyl)benzylamine	H	578	579	Y		7.59
2	2,4-Dichlorobenzaldehyde	2-(trifluoromethyl)benzylamine	Phenylacetic	682	683	Y		29.27
3	2,4-Dichlorobenzaldehyde	2-(trifluoromethyl)benzylamine	Benzoic	668	669	Y		65.55
4	2,4-Dichlorobenzaldehyde	2-(trifluoromethyl)benzylamine	IBP	752	753	Y		no fit

5	2,4-Dichlorobenzaldehyde	2-ethoxybenzylamine	H	554	555	Y		0.48
6	2,4-Dichlorobenzaldehyde	2-ethoxybenzylamine	Phenylacetic	658	659	Y		5.54
7	2,4-Dichlorobenzaldehyde	2-ethoxybenzylamine	Benzoic	644	645	Y		4.56
8	2,4-Dichlorobenzaldehyde	2-ethoxybenzylamine	IBP	728	729	Y		13.84
9	2,4-Dichlorobenzaldehyde	2-methoxyphenethylamine	H	554	555	Y	1.103	0.7
10	2,4-Dichlorobenzaldehyde	2-methoxyphenethylamine	Phenylacetic	658	659	Y	2.926	4.88
11	2,4-Dichlorobenzaldehyde	2-methoxyphenethylamine	Benzoic	644	645	Y	1.803	3.48
12	2,4-Dichlorobenzaldehyde	2-methoxyphenethylamine	IBP	728	729	Y	11.741	34.45
13	2,4-Dichlorobenzaldehyde	3-chlorophenethylamine	H	558	559	Y	2.185	1.18
14	2,4-Dichlorobenzaldehyde	3-chlorophenethylamine	Phenylacetic	662	663	Y	3.228	2.92

15	2,4-Dichlorobenzaldehyde	3-chlorophenethylamine	Benzoic	648	649	Y	6.409	6.93
16	2,4-Dichlorobenzaldehyde	3-chlorophenethylamine	IBP	732	733	Y	no fit	33.41
17	2,4-Dichlorobenzaldehyde	3-methoxybenzylamine	H	540	541	Y	3.083	1.63
18	2,4-Dichlorobenzaldehyde	3-methoxybenzylamine	Phenylacetic	644	645	Y	4.974	8.22
19	2,4-Dichlorobenzaldehyde	3-methoxybenzylamine	Benzoic	630	631	Y	3.274	7.31
20	2,4-Dichlorobenzaldehyde	3-methoxybenzylamine	IBP	714	715	Y	27.444	38.09
21	2,4-Dichlorobenzaldehyde	4-methoxybenzylamine	H	540	541	Y	1.121	1.57
22	2,4-Dichlorobenzaldehyde	4-methoxybenzylamine	Phenylacetic	644	645	Y	3.563	5.02
23	2,4-Dichlorobenzaldehyde	4-methoxybenzylamine	Benzoic	630	631	Y	3.187	6.14
24	2,4-Dichlorobenzaldehyde	4-methoxybenzylamine	IBP	714	715	Y	25.549	37.48

25	2,4-Dichlorobenzaldehyde	4-methoxyphenethylamine	H	554	555	Y	1.386	0.52
26	2,4-Dichlorobenzaldehyde	4-methoxyphenethylamine	Phenylacetic	658	659	Y	3.947	2.52
27	2,4-Dichlorobenzaldehyde	4-methoxyphenethylamine	Benzoic	644	645	Y	2.654	2.6
28	2,4-Dichlorobenzaldehyde	4-methoxyphenethylamine	IBP	728	729	Y	13.937	7.42
29	2,4-Dichlorobenzaldehyde	Benzylamine	H	510	511	Y	5.658	4.4
30	2,4-Dichlorobenzaldehyde	Benzylamine	Phenylacetic	614	615	Y	5.392	6.21
31	2,4-Dichlorobenzaldehyde	Benzylamine	Benzoic	600	601	Y	3.896	7.03
32	2,4-Dichlorobenzaldehyde	Benzylamine	IBP	684	685	Y	28.308	32.08
33	2,4-Dichlorobenzaldehyde	Cycloheptylamine	H	516	517	Y	1.901	0.72
34	2,4-Dichlorobenzaldehyde	Cycloheptylamine	Phenylacetic	620	621	Y	3.551	4.42

35	2,4-Dichlorobenzaldehyde	Cycloheptylamine	Benzoic	606	607	Y	2.169	5.67
36	2,4-Dichlorobenzaldehyde	Cycloheptylamine	IBP	690	691	Y	8.654	9.92
37	2,4-Dichlorobenzaldehyde	Cyclohexylamine	H	502	503	Y	0.992	1.3
38	2,4-Dichlorobenzaldehyde	Cyclohexylamine	Phenylacetic	606	607	Y	1.916	3.96
39	2,4-Dichlorobenzaldehyde	Cyclohexylamine	Benzoic	592	593	Y	2.12	4.37
40	2,4-Dichlorobenzaldehyde	Cyclohexylamine	IBP	676	677	Y	8.638	17.48
41	3,5-Bis(trifluoromethyl)benzaldehyde	2-(trifluoromethyl)benzylamine	H	646	647	Y	34.166	15.56
42	3,5-Bis(trifluoromethyl)benzaldehyde	2-(trifluoromethyl)benzylamine	Phenylacetic	750	751	Y	32.808	30.25
43	3,5-Bis(trifluoromethyl)benzaldehyde	2-(trifluoromethyl)benzylamine	Benzoic	736	737	Y	56.885	41.96
44	3,5-Bis(trifluoromethyl)benzaldehyde	2-(trifluoromethyl)benzylamine	IBP	820	821	Y	no fit	no fit

45	3,5-Bis(trifluoromethyl)benzaldehyde	2-ethoxybenzylamine	H	622	623	Y	6.34	0.92
46	3,5-Bis(trifluoromethyl)benzaldehyde	2-ethoxybenzylamine	Phenylacetic	726	727	Y	6.545	4.25
47	3,5-Bis(trifluoromethyl)benzaldehyde	2-ethoxybenzylamine	Benzoic	712	713	Y	7.744	7.51
48	3,5-Bis(trifluoromethyl)benzaldehyde	2-ethoxybenzylamine	IBP	796	797	Y	33.523	38.82
49	3,5-Bis(trifluoromethyl)benzaldehyde	2-methoxyphenethylamine	H	622	623	Y	3.768	0.32
50	3,5-Bis(trifluoromethyl)benzaldehyde	2-methoxyphenethylamine	Phenylacetic	726	727	Y	8.086	4.94
51	3,5-Bis(trifluoromethyl)benzaldehyde	2-methoxyphenethylamine	Benzoic	712	713	Y	6.448	2.16
52	3,5-Bis(trifluoromethyl)benzaldehyde	2-methoxyphenethylamine	IBP	796	797	Y	22.082	17.47
53	3,5-Bis(trifluoromethyl)benzaldehyde	3-chlorophenethylamine	H	626	627	Y	9.779	0.64
54	3,5-Bis(trifluoromethyl)benzaldehyde	3-chlorophenethylamine	Phenylacetic	730	731	Y	9.813	3.06

55	3,5-Bis(trifluoromethyl)benzaldehyde	3-chlorophenethylamine	Benzoic	716	717	Y	12.493	3.12
56	3,5-Bis(trifluoromethyl)benzaldehyde	3-chlorophenethylamine	IBP	800	801	Y	no fit	42.56
57	3,5-Bis(trifluoromethyl)benzaldehyde	3-methoxybenzylamine	H	608	609	Y	7.702	1.55
58	3,5-Bis(trifluoromethyl)benzaldehyde	3-methoxybenzylamine	Phenylacetic	712	713	Y	6.718	3.45
59	3,5-Bis(trifluoromethyl)benzaldehyde	3-methoxybenzylamine	Benzoic	698	699	Y	9.641	6.76
60	3,5-Bis(trifluoromethyl)benzaldehyde	3-methoxybenzylamine	IBP	782	783	Y	no fit	52.58
61	3,5-Bis(trifluoromethyl)benzaldehyde	4-methoxybenzylamine	H	608	609	Y	10.5	1.67
62	3,5-Bis(trifluoromethyl)benzaldehyde	4-methoxybenzylamine	Phenylacetic	712	713	Y	15.497	6.87
63	3,5-Bis(trifluoromethyl)benzaldehyde	4-methoxybenzylamine	Benzoic	698	699	Y	14.465	5.34
64	3,5-Bis(trifluoromethyl)benzaldehyde	4-methoxybenzylamine	IBP	782	783	Y	34.482	45.45

65	3,5-Bis(trifluoromethyl)benzaldehyde	4-methoxyphenethylamine	H	622	623	Y	3.304	0.26
66	3,5-Bis(trifluoromethyl)benzaldehyde	4-methoxyphenethylamine	Phenylacetic	726	727	Y	10.524	3.2
67	3,5-Bis(trifluoromethyl)benzaldehyde	4-methoxyphenethylamine	Benzoic	712	713	Y	0.033	5.21
68	3,5-Bis(trifluoromethyl)benzaldehyde	4-methoxyphenethylamine	IBP	796	797	Y	no fit	17.66
69	3,5-Bis(trifluoromethyl)benzaldehyde	Benzylamine	H	578	579	Y	9.449	0.64
70	3,5-Bis(trifluoromethyl)benzaldehyde	Benzylamine	Phenylacetic	682	683	Y	18.286	9.29
71	3,5-Bis(trifluoromethyl)benzaldehyde	Benzylamine	Benzoic	668	669	Y	17.03	9.06
72	3,5-Bis(trifluoromethyl)benzaldehyde	Benzylamine	IBP	752	753	Y	no fit	44.21
73	3,5-Bis(trifluoromethyl)benzaldehyde	Cycloheptylamine	H	584	585	Y	5.769	1.01
74	3,5-Bis(trifluoromethyl)benzaldehyde	Cycloheptylamine	Phenylacetic	688	689	Y	11.233	4.57

75	3,5-Bis(trifluoromethyl)benzaldehyde	Cycloheptylamine	Benzoic	674	675	Y	1.917	3.24
76	3,5-Bis(trifluoromethyl)benzaldehyde	Cycloheptylamine	IBP	758	759	Y	no fit	54.4
77	3,5-Bis(trifluoromethyl)benzaldehyde	Cyclohexylamine	H	570	571	Y	3.863	0.63
78	3,5-Bis(trifluoromethyl)benzaldehyde	Cyclohexylamine	Phenylacetic	674	675	Y	6.275	4.26
79	3,5-Bis(trifluoromethyl)benzaldehyde	Cyclohexylamine	Benzoic	660	661	Y	10.396	4.99
80	3,5-Bis(trifluoromethyl)benzaldehyde	Cyclohexylamine	IBP	744	745	Y	23.708	26.99
81	3-Phenoxybenzaldehyde	2-(trifluoromethyl)benzylamine	H	602	603	Y	10.768	9.87
82	3-Phenoxybenzaldehyde	2-(trifluoromethyl)benzylamine	Phenylacetic	706	707	Y	no fit	42.86
83	3-Phenoxybenzaldehyde	2-(trifluoromethyl)benzylamine	Benzoic	692	693	Y	31.546	no fit
84	3-Phenoxybenzaldehyde	2-(trifluoromethyl)benzylamine	IBP	776	777	Y	no fit	no fit

85	3-Phenoxybenzaldehyde	2-ethoxybenzylamine	H	578	579	Y	2.434	2.17
86	3-Phenoxybenzaldehyde	2-ethoxybenzylamine	Phenylacetic	682	683	Y	11.848	16.21
87	3-Phenoxybenzaldehyde	2-ethoxybenzylamine	Benzoic	668	669	Y	6.652	11.18
88	3-Phenoxybenzaldehyde	2-ethoxybenzylamine	IBP	752	753	Y	36.516	no fit
89	3-Phenoxybenzaldehyde	2-methoxyphenethylamine	H	578	579	Y	1.26	0.73
90	3-Phenoxybenzaldehyde	2-methoxyphenethylamine	Phenylacetic	682	683	Y	3.524	4.06
91	3-Phenoxybenzaldehyde	2-methoxyphenethylamine	Benzoic	668	669	Y	3.206	2.74
92	3-Phenoxybenzaldehyde	2-methoxyphenethylamine	IBP	752	753	Y	42.645	no fit
93	3-Phenoxybenzaldehyde	3-chlorophenethylamine	H	582	583	Y	6.302	3.8
94	3-Phenoxybenzaldehyde	3-chlorophenethylamine	Phenylacetic	686	687	Y	16.888	8.2

95	3-Phenoxybenzaldehyde	3-chlorophenethylamine	Benzoic	672	673	Y	8.663	5.26
96	3-Phenoxybenzaldehyde	3-chlorophenethylamine	IBP	756	757	Y	no fit	50.55
97	3-Phenoxybenzaldehyde	3-methoxybenzylamine	H	564	565	Y	4.51	2.5
98	3-Phenoxybenzaldehyde	3-methoxybenzylamine	Phenylacetic	668	669	Y	13.154	9.61
99	3-Phenoxybenzaldehyde	3-methoxybenzylamine	Benzoic	654	655	Y	5.859	6.93
100	3-Phenoxybenzaldehyde	3-methoxybenzylamine	IBP	738	739	Y	no fit	no fit
101	3-Phenoxybenzaldehyde	4-methoxybenzylamine	H	564	565	Y	2.496	1.26
102	3-Phenoxybenzaldehyde	4-methoxybenzylamine	Phenylacetic	668	669	Y	12.229	6.91
103	3-Phenoxybenzaldehyde	4-methoxybenzylamine	Benzoic	654	655	Y	8.135	7.48
104	3-Phenoxybenzaldehyde	4-methoxybenzylamine	IBP	738	739	Y	no fit	46.21

105	3-Phenoxybenzaldehyde	4-methoxyphenethylamine	H	578	579	Y	3.71	2.68
106	3-Phenoxybenzaldehyde	4-methoxyphenethylamine	Phenylacetic	682	683	Y	12.947	10.04
107	3-Phenoxybenzaldehyde	4-methoxyphenethylamine	Benzoic	668	669	Y	6.548	8.21
108	3-Phenoxybenzaldehyde	4-methoxyphenethylamine	IBP	752	753	Y	no fit	49.18
109	3-Phenoxybenzaldehyde	Benzylamine	H	534	535	Y	3.063	0.91
110	3-Phenoxybenzaldehyde	Benzylamine	Phenylacetic	638	639	Y	11.106	10.04
111	3-Phenoxybenzaldehyde	Benzylamine	Benzoic	624	625	Y	7.735	13.11
112	3-Phenoxybenzaldehyde	Benzylamine	IBP	708	709	Y	no fit	51.34
113	3-Phenoxybenzaldehyde	Cycloheptylamine	H	540	541	Y	2.955	1.78
114	3-Phenoxybenzaldehyde	Cycloheptylamine	Phenylacetic	644	645	Y	8.96	4.83

115	3-Phenoxybenzaldehyde	Cycloheptylamine	Benzoic	630	631	Y	3.712	5.6
116	3-Phenoxybenzaldehyde	Cycloheptylamine	IBP	714	715	Y	53.662	no fit
117	3-Phenoxybenzaldehyde	Cyclohexylamine	H	526	527	Y	1.935	1.27
118	3-Phenoxybenzaldehyde	Cyclohexylamine	Phenylacetic	630	631	Y	8.444	4.49
119	3-Phenoxybenzaldehyde	Cyclohexylamine	Benzoic	616	617	Y	5.008	4.77
120	3-Phenoxybenzaldehyde	Cyclohexylamine	IBP	700	701	Y	25.013	58.77
121	4-Phenoxybenzaldehyde	2-(trifluoromethyl)benzylamine	H	602	603	Y	8.135	27.78
122	4-Phenoxybenzaldehyde	2-(trifluoromethyl)benzylamine	Phenylacetic	706	707	Y	no fit	55.54
123	4-Phenoxybenzaldehyde	2-(trifluoromethyl)benzylamine	Benzoic	692	693	Y	17.576	no fit
124	4-Phenoxybenzaldehyde	2-(trifluoromethyl)benzylamine	IBP	776	777	Y	no fit	no fit

125	4-Phenoxybenzaldehyde	2-ethoxybenzylamine	H	578	579	Y	0.7	8.08
126	4-Phenoxybenzaldehyde	2-ethoxybenzylamine	Phenylacetic	682	683	Y	6.428	18.69
127	4-Phenoxybenzaldehyde	2-ethoxybenzylamine	Benzoic	668	669	Y	2.135	26.79
128	4-Phenoxybenzaldehyde	2-ethoxybenzylamine	IBP	752	753	Y	25.006	no fit
129	4-Phenoxybenzaldehyde	2-methoxyphenethylamine	H	578	579	Y	0.146	5.58
130	4-Phenoxybenzaldehyde	2-methoxyphenethylamine	Phenylacetic	682	683	Y	4.632	13.37
131	4-Phenoxybenzaldehyde	2-methoxyphenethylamine	Benzoic	668	669	Y	1.645	14.59
132	4-Phenoxybenzaldehyde	2-methoxyphenethylamine	IBP	752	753	Y	27.369	no fit
133	4-Phenoxybenzaldehyde	3-chlorophenethylamine	H	582	583	Y	5.802	15.92
134	4-Phenoxybenzaldehyde	3-chlorophenethylamine	Phenylacetic	686	687	Y	40.222	no fit

135	4-Phenoxybenzaldehyde	3-chlorophenethylamine	Benzoic	672	673	Y	10.053	45.97
136	4-Phenoxybenzaldehyde	3-chlorophenethylamine	IBP	756	757	Y	no fit	no fit
137	4-Phenoxybenzaldehyde	3-methoxybenzylamine	H	564	565	Y	1.207	5.26
138	4-Phenoxybenzaldehyde	3-methoxybenzylamine	Phenylacetic	668	669	Y	10.559	16.64
139	4-Phenoxybenzaldehyde	3-methoxybenzylamine	Benzoic	654	655	Y	0.788	12.57
140	4-Phenoxybenzaldehyde	3-methoxybenzylamine	IBP	738	739	Y	36.973	no fit
141	4-Phenoxybenzaldehyde	4-methoxybenzylamine	H	564	565	Y	2.042	4.21
142	4-Phenoxybenzaldehyde	4-methoxybenzylamine	Phenylacetic	668	669	Y	4.378	11.26
143	4-Phenoxybenzaldehyde	4-methoxybenzylamine	Benzoic	654	655	Y	2.355	14.02
144	4-Phenoxybenzaldehyde	4-methoxybenzylamine	IBP	738	739	Y	no fit	no fit

145	4-Phenoxybenzaldehyde	4-methoxyphenethylamine	H	578	579	Y	2.046	3.47
146	4-Phenoxybenzaldehyde	4-methoxyphenethylamine	Phenylacetic	682	683	Y	8.205	16.76
147	4-Phenoxybenzaldehyde	4-methoxyphenethylamine	Benzoic	668	669	Y	1.626	8.5
148	4-Phenoxybenzaldehyde	4-methoxyphenethylamine	IBP	752	753	Y	no fit	no fit
149	4-Phenoxybenzaldehyde	Benzylamine	H	534	535	Y	2.858	2.69
150	4-Phenoxybenzaldehyde	Benzylamine	Phenylacetic	638	639	Y	9.417	16.28
151	4-Phenoxybenzaldehyde	Benzylamine	Benzoic	624	625	Y	1.813	14.69
152	4-Phenoxybenzaldehyde	Benzylamine	IBP	708	709	Y	no fit	no fit
153	4-Phenoxybenzaldehyde	Cycloheptylamine	H	540	541	Y	0.772	4.09
154	4-Phenoxybenzaldehyde	Cycloheptylamine	Phenylacetic	644	645	Y	4.852	7.52

155	4-Phenoxybenzaldehyde	Cycloheptylamine	Benzoic	630	631	Y	2.031	8.94
156	4-Phenoxybenzaldehyde	Cycloheptylamine	IBP	714	715	Y	18.583	no fit
157	4-Phenoxybenzaldehyde	Cyclohexylamine	H	526	527	Y	1.115	4.11
158	4-Phenoxybenzaldehyde	Cyclohexylamine	Phenylacetic	630	631	Y	2.74	6.71
159	4-Phenoxybenzaldehyde	Cyclohexylamine	Benzoic	616	617	Y	1.397	9.82
160	4-Phenoxybenzaldehyde	Cyclohexylamine	IBP	700	701	Y	17.528	no fit
161	4-Propoxybenzaldehyde	2-(trifluoromethyl)benzylamine	H	568	569	Y	7.981	11
162	4-Propoxybenzaldehyde	2-(trifluoromethyl)benzylamine	Phenylacetic	672	673	Y	19.061	18.41
163	4-Propoxybenzaldehyde	2-(trifluoromethyl)benzylamine	Benzoic	658	659	Y	2.732	22.61
164	4-Propoxybenzaldehyde	2-(trifluoromethyl)benzylamine	IBP	742	743	Y	no fit	no fit

165	4-Propoxybenzaldehyde	2-ethoxybenzylamine	H	544	545	Y	0.994	5.06
166	4-Propoxybenzaldehyde	2-ethoxybenzylamine	Phenylacetic	648	649	Y	6.815	8.58
167	4-Propoxybenzaldehyde	2-ethoxybenzylamine	Benzoic	634	635	Y	2.16	7.03
168	4-Propoxybenzaldehyde	2-ethoxybenzylamine	IBP	718	719	Y	21.754	44.44
169	4-Propoxybenzaldehyde	2-methoxyphenethylamine	H	544	545	Y	0.518	5.34
170	4-Propoxybenzaldehyde	2-methoxyphenethylamine	Phenylacetic	648	649	Y	1.772	7.34
171	4-Propoxybenzaldehyde	2-methoxyphenethylamine	Benzoic	634	635	Y	1.1	4.8
172	4-Propoxybenzaldehyde	2-methoxyphenethylamine	IBP	718	719	Y	15.681	39.65
173	4-Propoxybenzaldehyde	3-chlorophenethylamine	H	548	549	Y	1.963	4.22
174	4-Propoxybenzaldehyde	3-chlorophenethylamine	Phenylacetic	652	653	Y	4.297	5.42

175	4-Propoxybenzaldehyde	3-chlorophenethylamine	Benzoic	638	639	Y	4.14	6.08
176	4-Propoxybenzaldehyde	3-chlorophenethylamine	IBP	722	723	Y	21.873	no fit
177	4-Propoxybenzaldehyde	3-methoxybenzylamine	H	530	531	Y	0.739	5.07
178	4-Propoxybenzaldehyde	3-methoxybenzylamine	Phenylacetic	634	635	Y	2.175	8.13
179	4-Propoxybenzaldehyde	3-methoxybenzylamine	Benzoic	620	621	Y	0.998	5.48
180	4-Propoxybenzaldehyde	3-methoxybenzylamine	IBP	704	705	Y	8.189	47.14
181	4-Propoxybenzaldehyde	4-methoxybenzylamine	H	530	531	Y	0.468	6.83
182	4-Propoxybenzaldehyde	4-methoxybenzylamine	Phenylacetic	634	635	Y	1.476	4.11
183	4-Propoxybenzaldehyde	4-methoxybenzylamine	Benzoic	620	621	Y	1.089	4.95
184	4-Propoxybenzaldehyde	4-methoxybenzylamine	IBP	704	705	Y	17.019	27.94

185	4-Propoxybenzaldehyde	4-methoxyphenethylamine	H	544	545	Y	0.542	4.26
186	4-Propoxybenzaldehyde	4-methoxyphenethylamine	Phenylacetic	648	649	Y	2.809	8.09
187	4-Propoxybenzaldehyde	4-methoxyphenethylamine	Benzoic	634	635	Y	1.069	1.47
188	4-Propoxybenzaldehyde	4-methoxyphenethylamine	IBP	718	719	Y	7.902	19.99
189	4-Propoxybenzaldehyde	Benzylamine	H	500	501	Y	0.869	2.31
190	4-Propoxybenzaldehyde	Benzylamine	Phenylacetic	604	605	Y	1.443	5.42
191	4-Propoxybenzaldehyde	Benzylamine	Benzoic	590	591	Y	1.949	5.53
192	4-Propoxybenzaldehyde	Benzylamine	IBP	674	675	Y	11.374	15.98
193	4-Propoxybenzaldehyde	Cycloheptylamine	H	506	507	Y	1.639	6.59
194	4-Propoxybenzaldehyde	Cycloheptylamine	Phenylacetic	610	611	Y	3.861	5.09

195	4-Propoxybenzaldehyde	Cycloheptylamine	Benzoic	596	597	Y	1.382	4.07
196	4-Propoxybenzaldehyde	Cycloheptylamine	IBP	680	681	Y	13.28	37.02
197	4-Propoxybenzaldehyde	Cyclohexylamine	H	492	493	Y	0.419	12.62
198	4-Propoxybenzaldehyde	Cyclohexylamine	Phenylacetic	596	597	Y	2.998	3.68
199	4-Propoxybenzaldehyde	Cyclohexylamine	Benzoic	582	583	Y	1.291	5.15
200	4-Propoxybenzaldehyde	Cyclohexylamine	IBP	666	667	Y	7.589	16.84
201	2-Bromobenzaldehyde	2-(trifluoromethyl)benzylamine	H	588	589	Y	no fit	no fit
202	2-Bromobenzaldehyde	2-(trifluoromethyl)benzylamine	Phenylacetic	692	693	Y	21.849	34.09
203	2-Bromobenzaldehyde	2-(trifluoromethyl)benzylamine	Benzoic	678	679	Y	30.209	39.59
204	2-Bromobenzaldehyde	2-(trifluoromethyl)benzylamine	IBP	762	763	Y	no fit	no fit

205	2-Bromobenzaldehyde	2-ethoxybenzylamine	H	564	565	Y	2.334	1.5
206	2-Bromobenzaldehyde	2-ethoxybenzylamine	Phenylacetic	668	669	Y	7.045	6.2
207	2-Bromobenzaldehyde	2-ethoxybenzylamine	Benzoic	654	655	Y	7.675	6.43
208	2-Bromobenzaldehyde	2-ethoxybenzylamine	IBP	738	739	Y	34.365	21.12
209	2-Bromobenzaldehyde	2-methoxyphenethylamine	H	564	565	Y	1.707	1.37
210	2-Bromobenzaldehyde	2-methoxyphenethylamine	Phenylacetic	668	669	Y	3.704	4.43
211	2-Bromobenzaldehyde	2-methoxyphenethylamine	Benzoic	654	655	Y	3.561	4.21
212	2-Bromobenzaldehyde	2-methoxyphenethylamine	IBP	738	739	Y	18.335	16.61
213	2-Bromobenzaldehyde	3-chlorophenethylamine	H	568	569	Y	6.48	2.06
214	2-Bromobenzaldehyde	3-chlorophenethylamine	Phenylacetic	672	673	Y	7.381	4.76

215	2-Bromobenzaldehyde	3-chlorophenethylamine	Benzoic	658	659	Y	8.508	6.43
216	2-Bromobenzaldehyde	3-chlorophenethylamine	IBP	742	743	Y	48.284	38.95
217	2-Bromobenzaldehyde	3-methoxybenzylamine	H	550	551	Y	5.563	2.42
218	2-Bromobenzaldehyde	3-methoxybenzylamine	Phenylacetic	654	655	Y	8.203	10.85
219	2-Bromobenzaldehyde	3-methoxybenzylamine	Benzoic	640	641	Y	10.287	9.59
220	2-Bromobenzaldehyde	3-methoxybenzylamine	IBP	724	725	Y	40.552	35.1
221	2-Bromobenzaldehyde	4-methoxybenzylamine	H	550	551	Y	6.605	1.83
222	2-Bromobenzaldehyde	4-methoxybenzylamine	Phenylacetic	654	655	Y	5.054	4.78
223	2-Bromobenzaldehyde	4-methoxybenzylamine	Benzoic	640	641	Y	10.555	8.22
224	2-Bromobenzaldehyde	4-methoxybenzylamine	IBP	724	725	Y	31.491	22.67

225	2-Bromobenzaldehyde	4-methoxyphenethylamine	H	564	565	Y	4.522	2.04
226	2-Bromobenzaldehyde	4-methoxyphenethylamine	Phenylacetic	668	669	Y	5.165	3.42
227	2-Bromobenzaldehyde	4-methoxyphenethylamine	Benzoic	654	655	Y	4.489	3.71
228	2-Bromobenzaldehyde	4-methoxyphenethylamine	IBP	738	739	Y	17.699	8.79
229	2-Bromobenzaldehyde	Benzylamine	H	520	521	Y	8.629	1.29
230	2-Bromobenzaldehyde	Benzylamine	Phenylacetic	624	625	Y	6.478	5.46
231	2-Bromobenzaldehyde	Benzylamine	Benzoic	610	611	Y	11.028	9.13
232	2-Bromobenzaldehyde	Benzylamine	IBP	694	695	Y	32.732	23.43
233	2-Bromobenzaldehyde	Cycloheptylamine	H	526	527	Y	3.319	3.27
234	2-Bromobenzaldehyde	Cycloheptylamine	Phenylacetic	630	631	Y	4.407	5.28

235	2-Bromobenzaldehyde	Cycloheptylamine	Benzoic	616	617	Y	2.862	5.35
236	2-Bromobenzaldehyde	Cycloheptylamine	IBP	700	701	Y	13.958	18.05
237	2-Bromobenzaldehyde	Cyclohexylamine	H	512	513	Y	5.867	3.61
238	2-Bromobenzaldehyde	Cyclohexylamine	Phenylacetic	616	617	Y	2.782	5.22
239	2-Bromobenzaldehyde	Cyclohexylamine	Benzoic	602	603	Y	3.303	6.27
240	2-Bromobenzaldehyde	Cyclohexylamine	IBP	686	687	Y	8.985	9.9
241	2,4-Dichlorobenzaldehyde	2-methoxyphenethylamine	H	596	597	Y	no fit	no fit
242	2,4-Dichlorobenzaldehyde	2-methoxyphenethylamine	Phenylacetic	714	715	Y	no fit	no fit
243	2,4-Dichlorobenzaldehyde	2-methoxyphenethylamine	IBP	784	785	Y	no fit	no fit
244	2,4-Dichlorobenzaldehyde	3-chlorophenethylamine	H	600	601	Y	44.099	no fit

245	2,4-Dichlorobenzaldehyde	3-chlorophenethylamine	Phenylacetic	718	719	Y	no fit	no fit
246	2,4-Dichlorobenzaldehyde	3-chlorophenethylamine	Benzoic	704	705	Y	no fit	no fit
247	2,4-Dichlorobenzaldehyde	4-methoxybenzylamine	H	582	583	Y	no fit	no fit
248	2,4-Dichlorobenzaldehyde	4-methoxybenzylamine	Phenylacetic	700	701	Y	no fit	no fit
249	2,4-Dichlorobenzaldehyde	4-methoxybenzylamine	Benzoic	686	687	Y	no fit	no fit
250	2,4-Dichlorobenzaldehyde	4-methoxyphenethylamine	H	596	597	Y	no fit	no fit
251	2,4-Dichlorobenzaldehyde	4-methoxyphenethylamine	Phenylacetic	714	715	Y	no fit	no fit
252	2,4-Dichlorobenzaldehyde	4-methoxyphenethylamine	Benzoic	700	701	Y	no fit	no fit
253	3,5-Bis(trifluoromethyl)benzaldehyde	2-methoxyphenethylamine	H	664	665	Y	no fit	no fit
254	3,5-Bis(trifluoromethyl)benzaldehyde	2-methoxyphenethylamine	Phenylacetic	782	783	Y	no fit	no fit

255	3,5-Bis(trifluoromethyl)benzaldehyde	2-methoxyphenethylamine	Benzoic	768	769	Y	no fit	no fit
256	3,5-Bis(trifluoromethyl)benzaldehyde	3-chlorophenethylamine	H	668	669	Y	no fit	no fit
257	3,5-Bis(trifluoromethyl)benzaldehyde	3-chlorophenethylamine	Phenylacetic	786	787	Y	no fit	no fit
258	3,5-Bis(trifluoromethyl)benzaldehyde	3-chlorophenethylamine	IBP	856	857	Y	no fit	no fit
259	3,5-Bis(trifluoromethyl)benzaldehyde	4-methoxybenzylamine	H	650	651	Y	no fit	no fit
260	3,5-Bis(trifluoromethyl)benzaldehyde	4-methoxybenzylamine	Phenylacetic	768	769	Y	no fit	no fit
261	3,5-Bis(trifluoromethyl)benzaldehyde	4-methoxybenzylamine	Benzoic	754	755	Y	no fit	no fit
262	3,5-Bis(trifluoromethyl)benzaldehyde	4-methoxyphenethylamine	H	664	665	Y	no fit	no fit
263	3,5-Bis(trifluoromethyl)benzaldehyde	4-methoxyphenethylamine	Phenylacetic	782	783	Y	no fit	no fit
264	3,5-Bis(trifluoromethyl)benzaldehyde	4-methoxyphenethylamine	Benzoic	768	769	Y	no fit	no fit

265	4-Phenoxybenzaldehyde	2-methoxyphenethylamine	H	620	621	Y	no fit	no fit
266	4-Phenoxybenzaldehyde	2-methoxyphenethylamine	Phenylacetic	738	739	Y	no fit	no fit
267	4-Phenoxybenzaldehyde	2-methoxyphenethylamine	Benzoic	892	893	Y	no fit	no fit
268	4-Phenoxybenzaldehyde	3-chlorophenethylamine	H	624	625	Y	no fit	no fit
269	4-Phenoxybenzaldehyde	3-chlorophenethylamine	Phenylacetic	742	743	Y	no fit	no fit
270	4-Phenoxybenzaldehyde	3-chlorophenethylamine	Benzoic	728	729	Y	no fit	no fit
271	4-Phenoxybenzaldehyde	4-methoxybenzylamine	H	606	607	Y	no fit	no fit
272	4-Phenoxybenzaldehyde	4-methoxybenzylamine	Phenylacetic	724	725	Y	no fit	no fit
273	4-Phenoxybenzaldehyde	4-methoxybenzylamine	IBP	794	795	Y	no fit	no fit
274	4-Phenoxybenzaldehyde	4-methoxyphenethylamine	H	620	621	Y	no fit	no fit

275	4-Phenoxybenzaldehyde	4-methoxyphenethylamine	Phenylacetic	738	739	Y	no fit	no fit
276	4-Phenoxybenzaldehyde	4-methoxyphenethylamine	Benzoic	724	725	Y	no fit	no fit
277	4-Propoxybenzaldehyde	2-methoxyphenethylamine	H	586	587	Y	no fit	no fit
278	4-Propoxybenzaldehyde	2-methoxyphenethylamine	Phenylacetic	704	705	Y	no fit	no fit
279	4-Propoxybenzaldehyde	2-methoxyphenethylamine	Benzoic	690	691	Y	no fit	no fit
280	4-Propoxybenzaldehyde	3-chlorophenethylamine	H	590	591	Y	no fit	no fit
281	4-Propoxybenzaldehyde	3-chlorophenethylamine	Phenylacetic	708	709	Y	no fit	no fit
282	4-Propoxybenzaldehyde	3-chlorophenethylamine	Benzoic	694	695	Y	no fit	no fit
283	4-Propoxybenzaldehyde	4-methoxybenzylamine	H	572	573	Y	no fit	no fit
284	4-Propoxybenzaldehyde	4-methoxybenzylamine	Phenylacetic	690	691	Y	no fit	no fit

285	4-Propoxybenzaldehyde	4-methoxybenzylamine	Benzoic	676	677	Y	no fit	no fit
286	4-Propoxybenzaldehyde	4-methoxyphenethylamine	H	586	587	Y	no fit	no fit
287	4-Propoxybenzaldehyde	4-methoxyphenethylamine	Phenylacetic	704	705	Y	no fit	no fit
288	4-Propoxybenzaldehyde	4-methoxyphenethylamine	IBP	774	775	Y	no fit	no fit

TRG 2415						obs.(M+1)	>85%	MC-1	MC-4
Cmpd #	R1: Amino Acid	R2: Aldehydes	X: Amines	R8: acids	M.W.	M.W.	LCQ	IC50 μM	IC50 μM
1	(S)-2,5-Diaminopentanoic acid	4-butyramidobenzaldehyde	None (OH)	Cyclohexylacetic	520	521	Y	1.934	5.04
2	(S)-2,5-Diaminopentanoic acid	4-hydroxybenzaldehyde	None (OH)	Cyclohexylacetic	465	466	Y	2.24	0.94
3	(S)-2,5-Diaminopentanoic acid	4-Ethoxybenzaldehyde	None (OH)	Cyclohexylacetic	493	494	Y	1.443	2.38
4	(S)-2,5-Diaminopentanoic acid	4-n-Propoxybenzaldehyde	None (OH)	Cyclohexylacetic	507	508	Y	2.572	2.55
5	(S)-2,5-Diaminopentanoic acid	4-isopropoxybenzaldehyde	None (OH)	Cyclohexylacetic	507	508	Y	2.517	0.96
6	(S)-2,5-Diaminopentanoic acid	4-n-butoxybenzaldehyde	None (OH)	Cyclohexylacetic	521	522	Y	2.388	5
7	(S)-2,5-Diaminopentanoic acid	4-Ethylbenzaldehyde	None (OH)	Cyclohexylacetic	477	478	Y	4.805	2.13

TRG 2415						obs.(M+1)	>85%	MC-1	MC-4
8	(S)-2,5-Diaminopentanoic acid	4-Amylbenzaldehyde	None (OH)	Cyclohexylacetic	519	520	Y	6.213	13.81
9	(S)-2,5-Diaminopentanoic acid	4-hydroxybenzaldehyde	Ammonia	Cyclohexylacetic	464	465	Y	3	1.95
10	(S)-2,5-Diaminopentanoic acid	4-Ethoxybenzaldehyde	Ammonia	Cyclohexylacetic	492	493	Y	0.46	1.76
11	(S)-2,5-Diaminopentanoic acid	4-n-Propoxybenzaldehyde	Ammonia	Cyclohexylacetic	506	507	Y	0.441	1.52
12	(S)-2,5-Diaminopentanoic acid	4-n-butoxybenzaldehyde	Ammonia	Cyclohexylacetic	520	521	Y	0.677	3.89
13	(S)-2,5-Diaminopentanoic acid	4-Ethylbenzaldehyde	Ammonia	Cyclohexylacetic	476	477	Y	1.833	0.87
14	(S)-2,5-Diaminopentanoic acid	4-Amylbenzaldehyde	Ammonia	Cyclohexylacetic	518	519	Y	1.69	9.39
15	(S)-2,6-Diaminohexanoic acid	4-hydroxybenzaldehyde	Ammonia	Acetic	396	397	Y	no fit	63.91
16	(S)-2,6-Diaminohexanoic acid	4-Ethoxybenzaldehyde	Ammonia	Acetic	424	425	Y	1.331	3.99

TRG 2415						obs.(M+1)	>85%	MC-1	MC-4
17	(S)-2,6-Diaminohexanoic acid	4-n-Propoxybenzaldehyde	Ammonia	Acetic	438	439	Y	0.581	9.35
18	(S)-2,6-Diaminohexanoic acid	4-n-butoxybenzaldehyde	Ammonia	Acetic	452	453	Y	0.306	7.95
19	(S)-2,6-Diaminohexanoic acid	4-Ethylbenzaldehyde	Ammonia	Acetic	408	409	Y	1.461	2.04
20	(S)-2,6-Diaminohexanoic acid	4-Amylbenzaldehyde	Ammonia	Acetic	450	451	Y	0.273	4.54

		TRG 2419					
	R1 = (S)-2,5-Diaminopentanoic acid						
	R2 = 4-Acetimidobenzaldehyde						
	R8 = Succinic anhydride						
				obs.(M+1)	>85%	MC-1	MC-4
Cmpd #	X: Amine	R8: Amine	M.W.	M.W.	LCQ	IC50 µM	IC50 µM
1	Phenethylamine	Aniline	632	633	Y	0.110	3.01

		TRG 2419					
3	Phenethylamine	Benzylamine	646	647	Y	0.049	2.15
4	Phenethylamine	Diethylamine	612	613	Y	0.058	14.38
6	Ammonia	Benzylamine	542	543	Y	0.082	6.41
7	Ammonia	Diethylamine	508	509	Y	0.141	10.07
8	Ammonia	None (OH)	453	454	Y	1.088	6.91
9	Ammonia	Aniline	528	529	Y	0.239	10.00
10	Ammonia	t-Butylamine	508	509	Y	0.093	4.32
11	Ammonia	Ammonia	452	453	Y	0.199	18.40
12	Ammonia	Phenethylamine	556	557	Y	0.073	16.67

		TRG 2419					
13	Ammonia	Piperidine	520	521	Y	0.073	2.51

		TRG 2420						
	R1 = (S)-2,5-Diaminopentanoic acid							
	R2 = 4-Acetimidobenzaldehyde							
					obs.(M+1)	>85%	MC-1	MC-4
Cmpd #	X: Amine	R8: Anhydride	R8: Amine	M.W.	M.W.	LCQ	IC50 µM	IC50 µM
1	phenethylamine	glutaric anhydride	isopropyl amine	612	613	Y	0.046	1.50
2	phenethylamine	glutaric anhydride	benzyl amine	660	661	Y	0.076	4.05

		TRG 2420						
3	phenethylamine	glutaric anhydride	diethyl amine	626	627	Y	0.030	8.23
4	phenethylamine	glutaric anhydride	phenethylamine	674	675	Y	0.068	4.17
5	phenethylamine	3-oxabicyclo(3.1.0) hexane-2, 4-dione anhydride	Isopropyl amine	610	611	Y	0.043	9.88
6	phenethylamine	3-oxabicyclo(3.1.0) hexane-2, 4-dione anhydride	benzyl amine	658	659	Y	0.103	5.13
7	phenethylamine	3-oxabicyclo(3.1.0) hexane-2, 4-dione anhydride	diethyl amine	624	625	Y	0.063	1.81
8	phenethylamine	3-oxabicyclo(3.1.0) hexane-2, 4-dione anhydride	phenethylamine	672	673	Y	0.208	2.36
9	phenethylamine	diglycolic anhydride	Isopropyl amine	614	615	Y	0.040	3.23
10	phenethylamine	diglycolic anhydride	benzyl amine	662	663	Y	0.055	0.94
11	phenethylamine	diglycolic anhydride	diethyl amine	628	629	Y	0.028	4.63

		TRG 2420						
12	phenethylamine	diglycolic anhydride	phenethylamine	676	677	Y	0.079	1.53
13	phenethylamine	phthalic anhydride	isopropyl amine	646	647	Y	0.065	0.67
14	phenethylamine	phthalic anhydride	benzyl amine	694	695	Y	0.135	0.29
15	phenethylamine	phthalic anhydride	diethyl amine	660	661	Y	0.070	1.37
16	phenethylamine	phthalic anhydride	phenethylamine	708	709	Y	0.164	1.20
17	phenethylamine	3-(t-butyl dimethyl silyloxy) glutaric anhydride	isopropyl amine	584	585	Y	0.099	2.30
18	phenethylamine	3-(t-butyl dimethyl silyloxy) glutaric anhydride	benzyl amine	632	633	Y	0.057	3.40
19	phenethylamine	3-(t-butyl dimethyl silyloxy) glutaric anhydride	diethyl amine	598	599	Y	0.060	10.66
20	phenethylamine	3-(t-butyl dimethyl silyloxy) glutaric anhydride	phenethylamine	646	647	Y	0.123	7.59

		TRG 2420						
21	ammonia	glutaric anhydride	isopropyl amine	628	629	Y	0.023	4.18
22	ammonia	glutaric anhydride	benzyl amine	676	677	Y	0.027	43.99
23	ammonia	glutaric anhydride	diethyl amine	642	643	Y	0.020	2.65
24	ammonia	glutaric anhydride	phenethylamine	690	691	Y	0.118	13.47
25	ammonia	3-oxabicyclo(3.1.0) hexane-2, 4-dione anhydride	isopropyl amine	508	509	Y	0.103	4.82
26	ammonia	3-oxabicyclo(3.1.0) hexane-2, 4-dione anhydride	benzyl amine	556	557	Y	0.093	5.01
27	ammonia	3-oxabicyclo(3.1.0) hexane-2, 4-dione anhydride	diethyl amine	522	523	Y	0.040	4.19
28	ammonia	3-oxabicyclo(3.1.0) hexane-2, 4-dione anhydride	phenethylamine	570	571	Y	0.203	4.08
29	ammonia	diglycolic anhydride	isopropyl amine	506	507	Y	0.129	35.02

		TRG 2420						
30	ammonia	diglycolic anhydride	benzyl amine	554	555	Y	0.057	3.08
31	ammonia	diglycolic anhydride	diethyl amine	520	521	Y	0.121	48.31
32	ammonia	diglycolic anhydride	phenethylamine	568	569	Y	0.344	12.29
33	ammonia	phthalic anhydride	isopropyl amine	510	511	Y	0.307	4.30
34	ammonia	phthalic anhydride	benzyl amine	558	559	Y	0.271	0.94
35	ammonia	phthalic anhydride	diethyl amine	524	525	Y	0.218	1.42
36	ammonia	phthalic anhydride	phenethylamine	572	573	Y	0.257	0.54
37	ammonia	3-(t-butyl dimethyl silyloxy) glutaric anhydride	isopropyl amine	542	543	Y	0.186	2.17
38	ammonia	3-(t-butyl dimethyl silyloxy) glutaric anhydride	benzyl amine	590	591	Y	0.084	0.35

		TRG 2420						
39	ammonia	3-(t-butyl dimethyl silyloxy) glutaric anhydride	diethyl amine	556	557	Y	0.237	33.10
40	ammonia	3-(t-butyl dimethyl silyloxy) glutaric anhydride	phenethylamine	604	605	Y	0.460	12.11

		TRG 2421						
	R1 = L-Lysine				obs.(M+1)	>85%	MC-1	MC-4
Cmpd #	**R2: benzaldehyde**	**X: amine**	**R8: acid**	**M.W.**	**M.W.**	**LCQ**	**IC50 µM**	**IC50 µM**
1	3,5-bis(trifluoromethyl)benzaldehyde	phenethylamine	benzoic acid	683	684	Y	4.18	1.78
2	3,5-bis(trifluoromethyl)benzaldehyde	phenethylamine	p-toluic acid	697	698	Y	3.73	3.03
3	3,5-bis(trifluoromethyl)benzaldehyde	phenethylamine	4-bromobenzoic acid	762	763	Y	4.91	9.64
4	3,5-bis(trifluoromethyl)benzaldehyde	phenethylamine	p-anisic acid	713	714	Y	2.57	2.81
5	3,5-bis(trifluoromethyl)benzaldehyde	phenethylamine	4-biphenylcarboxylic acid	759	760	Y	11.24	9.41
6	3,5-bis(trifluoromethyl)benzaldehyde	tyramine	benzoic acid	699	700	Y	2.25	0.76
7	3,5-bis(trifluoromethyl)benzaldehyde	tyramine	p-toluic acid	713	714	Y	3.19	4.53

		TRG 2421						
8	3,5-bis(trifluoromethyl)benzaldehyde	tyramine	4-bromobenzoic acid	778	779	Y	5.00	5.99
9	3,5-bis(trifluoromethyl)benzaldehyde	tyramine	p-anisic acid	729	730	Y	1.50	1.75
10	3,5-bis(trifluoromethyl)benzaldehyde	tyramine	4-biphenylcarboxylic acid	775	776	Y	4.77	9.11
11	3,5-bis(trifluoromethyl)benzaldehyde	2-(4-methoxyphenyl)ethylamine	benzoic acid	713	714	Y		
12	3,5-bis(trifluoromethyl)benzaldehyde	2-(4-methoxyphenyl)ethylamine	p-toluic acid	727	728	Y	2.57	1.40
13	3,5-bis(trifluoromethyl)benzaldehyde	2-(4-methoxyphenyl)ethylamine	4-bromobenzoic acid	792	793	Y	4.41	8.11
14	3,5-bis(trifluoromethyl)benzaldehyde	2-(4-methoxyphenyl)ethylamine	p-anisic acid	743	744	Y	3.47	1.69
15	3,5-bis(trifluoromethyl)benzaldehyde	2-(4-methoxyphenyl)ethylamine	4-biphenylcarboxylic acid	789	790	Y	7.81	7.60
16	3,5-bis(trifluoromethyl)benzaldehyde	3, 4 dimethoxyphenylethylamine	benzoic acid	743	744	Y	2.42	0.36

		TRG 2421						
17	3,5-bis(trifluoromethyl)benzaldehyde	3, 4 dimethoxyphenylethylamine	p-toluic acid	757	758	Y	2.06	0.83
18	3,5-bis(trifluoromethyl)benzaldehyde	3, 4 dimethoxyphenylethylamine	4-bromobenzoic acid	822	823	Y	4.79	1.35
19	3,5-bis(trifluoromethyl)benzaldehyde	3, 4 dimethoxyphenylethylamine	p-anisic acid	773	774	Y	1.63	0.52
20	3,5-bis(trifluoromethyl)benzaldehyde	3, 4 dimethoxyphenylethylamine	4-biphenylcarboxylic acid	819	820	Y	4.22	1.97
21	3,5-bis(trifluoromethyl)benzaldehyde	4-ethoxyphenethylamine	benzoic acid	727	728	Y	2.59	3.98
22	3,5-bis(trifluoromethyl)benzaldehyde	4-ethoxyphenethylamine	p-toluic acid	741	742	Y	3.02	8.22
23	3,5-bis(trifluoromethyl)benzaldehyde	4-ethoxyphenethylamine	4-bromobenzoic acid	806	807	Y	7.44	8.22
24	3,5-bis(trifluoromethyl)benzaldehyde	4-ethoxyphenethylamine	p-anisic acid	757	758	Y	2.35	2.26
25	3,5-bis(trifluoromethyl)benzaldehyde	4-ethoxyphenethylamine	4-biphenylcarboxylic acid	803	804	Y	10.00	10.93

		TRG 2421						
26	3,5-bis(trifluoromethyl)benzaldehyde	4-phenoxyphenethylamine	benzoic acid	775	776	Y	11.39	12.91
27	3,5-bis(trifluoromethyl)benzaldehyde	4-phenoxyphenethylamine	p-toluic acid	789	790	Y	7.26	9.26
28	3,5-bis(trifluoromethyl)benzaldehyde	4-phenoxyphenethylamine	4-bromobenzoic acid	854	855	Y	15.74	
29	3,5-bis(trifluoromethyl)benzaldehyde	4-phenoxyphenethylamine	p-anisic acid	805	806	Y	5.10	7.92
30	3,5-bis(trifluoromethyl)benzaldehyde	4-phenoxyphenethylamine	4-biphenylcarboxylic acid	851	852	Y	36.36	
31	3,5-bis(trifluoromethyl)benzaldehyde	2-(4-chlorophenyl)ethylamine	benzoic acid	717	718	Y	5.90	2.77
32	3,5-bis(trifluoromethyl)benzaldehyde	2-(4-chlorophenyl)ethylamine	p-toluic acid	731	732	Y	5.77	4.15
33	3,5-bis(trifluoromethyl)benzaldehyde	2-(4-chlorophenyl)ethylamine	4-bromobenzoic acid	796	797	Y	6.93	8.36
34	3,5-bis(trifluoromethyl)benzaldehyde	2-(4-chlorophenyl)ethylamine	p-anisic acid	747	748	Y	4.98	2.64

		TRG 2421						
35	3,5-bis(trifluoromethyl)benzaldehyde	2-(4-chlorophenyl)ethylamine	4-biphenylcarboxylic acid	793	794	Y		
36	3,5-bis(trifluoromethyl)benzaldehyde	2-(3-methoxyphenyl)ethylamine	benzoic acid	713	714	Y	3.99	0.89
37	3,5-bis(trifluoromethyl)benzaldehyde	2-(3-methoxyphenyl)ethylamine	p-toluic acid	727	728	Y	3.08	0.84
38	3,5-bis(trifluoromethyl)benzaldehyde	2-(3-methoxyphenyl)ethylamine	4-bromobenzoic acid	792	793	Y	7.47	1.34
39	3,5-bis(trifluoromethyl)benzaldehyde	2-(3-methoxyphenyl)ethylamine	p-anisic acid	743	744	Y	3.30	1.04
40	3,5-bis(trifluoromethyl)benzaldehyde	2-(3-methoxyphenyl)ethylamine	4-biphenylcarboxylic acid	789	790	Y	12.10	3.98
41	3-(trifluoromethyl)benzaldehyde	phenethylamine	benzoic acid	615	616	Y	2.51	1.72
42	3-(trifluoromethyl)benzaldehyde	phenethylamine	p-anisic acid	645	646	Y	2.15	1.72
43	3-(trifluoromethyl)benzaldehyde	2-(4-methoxyphenyl)ethylamine	benzoic acid	645	646	Y	2.15	1.76

		TRG 2421						
44	3-(trifluoromethyl)benzaldehyde	2-(4-methoxyphenyl)ethylamine	p-anisic acid	675	676	Y	1.54	1.42
45	3-(trifluoromethyl)benzaldehyde	4-ethoxyphenethylamine	benzoic acid	659	660	Y	0.98	2.73
46	3-(trifluoromethyl)benzaldehyde	4-ethoxyphenethylamine	p-anisic acid	689	690	Y	1.58	3.61
47	3-(trifluoromethyl)benzaldehyde	2-(3-methoxyphenyl)ethylamine	benzoic acid	645	646	Y	2.71	1.37
48	3-(trifluoromethyl)benzaldehyde	2-(3-methoxyphenyl)ethylamine	p-anisic acid	675	676	Y	1.74	0.95

	TRG 2422			
Cmpd #	**R1: Amino Acid**	**R1a: Amino Acid**	**R2: Aldehyde**	**X: Amine**
1	Fmoc-5-Aminovaleric acid	t-Boc-L-glycine	4-acetamidobenzaldehyde	2-methoxybenzylamine

	TRG 2422			
2	Fmoc-5-Aminovaleric acid	t-Boc-L-glycine	4-acetamidobenzaldehyde	4-methoxybenzylamine
3	Fmoc-5-Aminovaleric acid	t-Boc-L-glycine	4-acetamidobenzaldehyde	cyclohexylamine
4	Fmoc-5-Aminovaleric acid	t-Boc-L-glycine	4-acetamidobenzaldehyde	phenethylamine
5	Fmoc-5-Aminovaleric acid	t-Boc-L-glycine	4-acetamidobenzaldehyde	ammonia

TRG 2424									
						obs.(M+1)	>85%	MC-1	MC-4
Cmpd #	R1	R2	X	R8	M.W.	M.W.	LCQ	IC50 µM	IC50 µM
								IC50	IC50
2424#1	L-ornithine	4-acetamidobenzaldehyde	ammonia	valeric acid	454	455	Y	0.19	53.95
2424#2	L-ornithine	4-acetamidobenzaldehyde	ammonia	4-phenoxybutyric acid	530	531	Y	0.05	7.77
2424#3	L-ornithine	4-acetamidobenzaldehyde	ammonia	glutaric anhydride	452	453	Y	0.09	3.04
2424#4	L-ornithine	4-acetamidobenzaldehyde	phenethylamine	valeric acid	558	559	Y	0.02	4.37
2424#5	L-ornithine	4-acetamidobenzaldehyde	phenethylamine	4-phenoxybutyric acid	634	635	Y	0.05	1.51
2424#6	L-ornithine	4-acetamidobenzaldehyde	phenethylamine	glutaric anhydride	556	557	Y	0.11	0.91

TRG 2424									
2424#7	L-lysine	4-acetamidobenzaldehyde	ammonia	valeric acid	468	469	Y	0.46	
2424#8	L-lysine	4-acetamidobenzaldehyde	ammonia	4-phenoxybutyric acid	544	545	Y	0.22	5.18
2424#9	L-lysine	4-acetamidobenzaldehyde	ammonia	glutaric anhydride	466	467	Y	0.19	3.25
2424#10	L-lysine	4-acetamidobenzaldehyde	phenethylamine	valeric acid	572	573	Y	0.08	12.86
2424#11	L-lysine	4-acetamidobenzaldehyde	phenethylamine	4-phenoxybutyric acid	648	649	Y	0.21	3.51
2424#12	L-lysine	4-acetamidobenzaldehyde	phenethylamine	glutaric anhydride	570	571	Y	0.14	0.78

Some of the isoquinoline compounds were further tested for binding to MCR-3 and MCR-5. Table 2 shows the IC50 values for some of the isoquinoline compounds shown in Table 1. As shown in Table 2, various isoquinoline compounds bound to MCR-3 and MCR-5. Several isoquinoline compounds exhibited similar affinities between all four MC receptors whereas other isoquinoline compounds showed specificity for at least one MC receptor over another MC receptor (compare Tables 1 and 2).

TABLE 2. Binding of Isoquinoline Compounds to MCR-3 and MCR-5

TABLE 2. *IN VITRO* MELANOCORTIN RECEPTOR PROFILE RECEPTOR BINDING RESULTS

Array/ Compound#	R1: Amino Acids	R2: Aldehydes	R3: amines	R4: Substit. on R1	MW	MC-3 IC50 (μM)	MC-5 IC50 (μM)
TRG 2403							
3	L-Lys	4-Acetamido-benzaldehyde	2-methoxybenzylamine		516	>10	>10
TRG 2404							
3	L-Lys	4-Bromobenz-aldehyde	2-methoxybenzylamine		552	0.9	1
TRG 2405							
64	Glycine	4-Cyanobenz-aldehyde	Cyclohexylamine		393		
77	Glycine	3-Methoxy-4-hydroxy-5-bromobenz-aldehyde	Cyclohexylamine		477	>10	>10
156	(S)-2,3-Diamino-propionic acid	4-Hydroxy-benzaldehyde	Cyclohexylamine		423	23.71	2.83

TABLE 2. *IN VITRO* MELANOCORTIN RECEPTOR PROFILE RECEPTOR BINDING RESULTS

Array/ Compound#	R1: Amino Acids	R2: Aldehydes	R3: amines	R4: Substit. on R1	MW	MC-3 IC50 (μM)	MC-5 IC50 (μM)
190	(S)-2,6-Diamino-hexanoic acid	2,4-Dichloro-benzaldehyde	Cyclohexylamine		518	2.24[2]	0.80
235	(S)-2,6-Diamino-hexanoic acid	4-(Dimethyl-amino) benzaldehyde	Cyclohexylamine		492	22.27	2.82
238	(S)-2,6-Diamino-hexanoic acid	4-(Trifluoro-methyl) benzaldehyde	Cyclohexylamine		517	>10	0.43
239	(S)-2,6-Diamino-hexanoic acid	4-Acetamido-benzaldehyde	Cyclohexylamine		492	39.79	8.72
241	(S)-2,6-Diamino-hexanoic acid	4-Biphenyl-carbox-aldehyde	Cyclohexylamine		525	7.45	1.04

TABLE 2. *IN VITRO* MELANOCORTIN RECEPTOR PROFILE RECEPTOR BINDING RESULTS

Array/ Compound#	R1: Amino Acids	R2: Aldehydes	R3: amines	R4: Substit. on R1	MW	MC-3 IC50 (μM)	MC-5 IC50 (μM)
242	(S)-2,6-Diamino-hexanoic acid	4-Bromobenz-aldehyde	Cyclohexylamine		528	0.55[2]	0.41
246	(S)-2,6-Diamino-hexanoic acid	4-Hydroxy-benzaldehyde	Cyclohexylamine		465	>10	>10
252	(S)-2,6-Diamino-hexanoic acid	4-Phenoxy-benzaldehyde	Cyclohexylamine		541	6.49	1.86
253	(S)-2,6-Diamino-hexanoic acid	4-Propoxy-benzaldehyde	Cyclohexylamine		507	9.68	2.77
262	(S)-2,6-Diamino-hexanoic acid	8-Hydroxy-quinoline-2-carbox-aldehyde	Cyclohexylamine			>10	>10

TABLE 2. *IN VITRO* MELANOCORTIN RECEPTOR PROFILE RECEPTOR BINDING RESULTS

Array/ Compound#	R1: Amino Acids	R2: Aldehydes	R3: amines	R4: Substit. on R1	MW	MC-3 IC50 (μM)	MC-5 IC50 (μM)
268	(S)-2,6-Diamino-hexanoic acid	4-Methoxy-3-(sulfonic acid)benz-aldehyde	Cyclohexylamine		559		
TRG 2407							
39	(S)-2,6-Diamino-hexanoic acid	2,4-Dichloro-benzaldehyde	Ammonia		435	0.28	0.24
67	(S)-2,6-Diamino-hexanoic acid	4-Acetamido-benzaldehyde	Cyclopentylamine		478	20.86	4.16
TRG 2408							
30	(R)-2,6-Diamino-hexanoic acid	4-Acetamido-benzaldehyde	Cyclohexylamine	Boc	491	40.43	9.35

TABLE 2. *IN VITRO* MELANOCORTIN RECEPTOR PROFILE RECEPTOR BINDING RESULTS

Array/ Compound#	R1: Amino Acids	R2: Aldehydes	R3: amines	R4: Substit. on R1	MW	MC-3 IC50 (μM)	MC-5 IC50 (μM)
57	(S)-2,5-Diamino-pentanoic acid	4-Acetamido-benzaldehyde	2-Methoxybenzylamine	Phenyl-acetic acid	591	5.17	1.70
62	(S)-2,5-Diamino-pentanoic acid	2,4-Dichloro-benzaldehyde	2-Methoxybenzylamine	Glycine	555	5.71	2.79
TRG 2409							
2	(S)-2,6-Diamino-hexanoic acid	4-Nitrobenz-aldehyde	2-Methoxybenzylamine	R5: Butyric Acid	543		
14	(S)-2,6-Diamino-hexanoic acid	4-Nitrobenz-aldehyde	Cyclohexylamine	R5: Butyric Acid	519		

These results show that isoquinoline compounds are MC receptor ligands.

EXAMPLE V

Effect of Isoquinoline Compounds on Melanocortin Receptor Signaling

This example shows the effect of isoquinoline compounds on MC receptor signaling.

Various isoquinoline compounds were tested for their ability to activate MC receptor by measuring cAMP as described in Example III. Table 3 shows the EC50 values, the effective concentration for achieving 50% of maximal cAMP production, for various isoquinoline compounds administered to HEK 293 cells expressing MCR-1, MCR-3, MCR-4 or MCR-5. The EC50 values shown in Table 3 are µM. Table 3 also shows the maximum amount (in pmol) of cAMP produced in response to a given isoquinoline compound. As shown in Table 3, isoquinoline compounds were able to activate various MC receptors with a range of affinities.

TABLE 3. *In vitro* Binding and Activation of Isoquinoline Compounds to Melanocortin Receptors

TABLE 3. *IN VITRO* MELANOCORTIN RECEPTOR PROFILE
Functional (cAMP) Results

Array/ Compound #	R1: Amino Acids	R2: Aldehydes	R3: amines	R4: Substit. on R1	MW	MC-1		MC-3 EC50	MC-4		MC-5 EC50
						EC50	Max (pmole)		EC50	Max (pmole)	
TRG 2403											
3	L-Lys	4-Acetamido-benzaldehyde	2-methoxybenzyl- amine		516	1.1	20		47.64	50.71	
TRG 2404											
3	L-Lys	4-Bromobenz-aldehyde	2-methoxybenzyl-amine		552	2.2	20				
TRG 2405											
64	Glycine	4-Cyanobenz-aldehyde	Cyclohexyl-amine		393						
77	Glycine	3-Methoxy-4-hydroxy-5-bromobenz-aldehyde	Cyclohexyl-amine		477	>50		>50	>50		>50
156	(S)-2,3-Diamino-propionic acid	4-Hydroxybenz-aldehyde	Cyclohexyl-amine		423	20.64	16.01	>50	>50		>50

TABLE 3. *IN VITRO* MELANOCORTIN RECEPTOR PROFILE
Functional (cAMP) Results

Array/ Compound #	R1: Amino Acids	R2: Aldehydes	R3: amines	R4: Substit. on R1	MW	MC-1		MC-3 EC50	MC-4		MC-5 EC50
						EC50	Max (pmole)		EC50	Max (pmole)	
190	(S)-2,6-Diamino-hexanoic acid	2,4-Dichloro-benzaldehyde	Cyclohexyl-amine		518	8.52	33.56		46.29	100.48	
235	(S)-2,6-Diamino-hexanoic acid	4-(Dimethyl-amino)benz-aldehyde	Cyclohexyl-amine		492	29.9	17.07		>50		
238	(S)-2,6-Diamino-hexanoic acid	4-(Trifluoro-methyl)benz-aldehyde	Cyclohexyl-amine		517	19.92	29.82	>50	>50		>50
239	(S)-2,6-Diamino-hexanoic acid	4-Acetamido-benzaldehyde	Cyclohexyl-amine		492	3.67	20.6	>50	>50		>50
241	(S)-2,6-Diamino-hexanoic acid	4-Biphenyl-carbox-aldehyde	Cyclohexyl-amine		525	10.36	66.67	>50	28.48	32.32	>50

TABLE 3. *IN VITRO* MELANOCORTIN RECEPTOR PROFILE
Functional (cAMP) Results

Array/ Compound #	R1: Amino Acids	R2: Aldehydes	R3: amines	R4: Substit. on R1	MW	MC-1		MC-3 EC50	MC-4		MC-5 EC50
						EC50	Max (pmole)		EC50	Max (pmole)	
242	(S)-2,6-Diamino-hexanoic acid	4-Bromobenz-aldehyde	Cyclohexyl-amine		528	13.05	55.89	>50	>50		>50
246	(S)-2,6-Diamino-hexanoic acid	4-Hydroxybenz-aldehyde	Cyclohexyl-amine		465	23.72	12.48	>50	>50		>50
252	(S)-2,6-Diamino-hexanoic acid	4-Phenoxybenz-aldehyde	Cyclohexyl-amine		541	15.97	33.07	>50	18.48	39.24	>50
253	(S)-2,6-Diamino-hexanoic acid	4-Propoxybenz-aldehyde	Cyclohexyl-amine		507	8.5	22.55	>50	16.61	69.11	>50
262	(S)-2,6-Diamino-hexanoic acid	8-Hydroxy-quinoline-2-carbox-aldehyde	Cyclohexyl-amine			>50		>50	>50		>50

TABLE 3. *IN VITRO* MELANOCORTIN RECEPTOR PROFILE Functional (cAMP) Results

Array/ Compound #	R1: Amino Acids	R2: Aldehydes	R3: amines	R4: Substit. on R1	MW	MC-1		MC-3 EC50	MC-4		MC-5 EC50
						EC50	Max (pmole)		EC50	Max (pmole)	
268	(S)-2,6-Diamino-hexanoic acid	4-Methoxy-3-(sulfonic acid)benz-aldehyde	Cyclohexyl-amine		559						
TRG 2407											
39	(S)-2,6-Diamino-hexanoic acid	2,4-Dichloroben z-aldehyde	Ammonia		435						
67	(S)-2,6-Diamino-hexanoic acid	4-Acetamido-benzaldehyde	Cyclopentyl-amine		478						
TRG 2408											
30	(R)-2,6-Diamino-hexanoic acid	4-Acetamido-benzaldehyde	Cyclohexyl-amine	Boc	491	2.83	125.79				
57	(S)-2,5-Diamino-pentanoic acid	4-Acetamido-benzaldehyde	2-Methoxy-benzylamine	Phenyl-acetic acid	591	<0.1					

TABLE 3. *IN VITRO* MELANOCORTIN RECEPTOR PROFILE
Functional (cAMP) Results

Array/ Compound #	R1: Amino Acids	R2: Aldehydes	R3: amines	R4: Substit. on R1	MW	MC-1		MC-3 EC50	MC-4		MC-5 EC50
						EC50	Max (pmole)		EC50	Max (pmole)	
62	(S)-2,5-Diamino-pentanoic acid	2,4-Dichlorobenz-aldehyde	2-Methoxy-benzylamine	Glycine	555	<0.1					
TRG 2409											
2	(S)-2,6-Diamino-hexanoic acid	4-Nitrobenz-aldehyde	2-Methoxy-benzylamine	R5: Butyric Acid	543	1.01 ± 0.26[3]	200				
14	(S)-2,6-Diamino-hexanoic acid	4-Nitrobenz-aldehyde	Cyclohexyl-amine	R5: Butyric Acid	519	0.87 ± 0.2[3]	170				

These results show that isoquinoline compounds are MC receptor ligands that can activate MC receptors.

EXAMPLE VI

Reduction of Lipopolysaccharide-Induced Tumor Necrosis Factor Levels in Mice

This example describes the effectiveness of isoquinoline compounds for decreasing tumor necrosis factor (TNF) levels in lipopolysaccharide (LPS; endotoxin) treated mice.

BALB/c female mice weighing approximately 20 g were placed into a control group and a treated group. Five mg/kg of LPS in 0.9% saline was administered (100 µl to give 100 µg LPS per mouse) by intraperitoneal (IP) injection to all mice. Mice in the treatment group received either 30, 100, 300 or 600 µg of various isoquinoline compounds per mouse in a volume of 100 µl of PBS. Control mice received 100 µl of saline alone. One minute after initial injections all mice received the LPS injection. As a positive control, 100 µg of HP 228 was injected per mouse.

Blood samples were collected from the orbital sinus of treated and control mice 90 minutes or 105 minutes after LPS administration. The plasma was separated by centrifugation at 3000 x g for 5 min and stored at -20°C. Samples were thawed and diluted, if TNF-α concentration was greater than 3200 pg/ml, with PBS containing 1% bovine serum albumin, 10% donor horse serum, 1% normal mouse serum, 0.05% TWEEN-20 and 0.05% thimerosal. A 100 µl sample of plasma was assayed by ELISA for TNF-α. Briefly, ELISA plates were coated with hamster anti-mouse TNF-α antibody (Genzyme;

Cambridge MA). Samples or known concentrations of TNF-α were added to the coated plates and incubated for 2 hr at 37°C. Plates were washed and subsequently incubated with biotinylated rabbit anti-mouse TNG-α for 1 hr at 37°C. Plates were washed and incubated with streptavidin-HRP for 1 hr at 37°C, and HRP activity was detected with hydrogen peroxide and o-phenylenediamine (OPD) using standard immunoassay procedures.

The mean (± SEM) TNF-α level in five mice from each group was determined and the percent reduction in TNF-α levels was calculated. As shown in Table 4, treatment of mice with various isoquinoline compounds decreased the levels of TNF-α in a dose dependent manner when compared to saline controls. TRG 2408-30 was particularly effective at inhibiting TNF-α using both i.p. and oral administration.

Table 4. Effect of Isoquinoline Compounds on Cytokines

TABLE 4.

IN VIVO MELANOCORTIN RECEPTOR PROFILE
In Vivo Cytokine Data for Compounds Received
90 or 105 Minutes

Array/ Compound #	% TNF-α Inhibition					% IL-10 Induction				
	IP			Oral		IP			Oral	
	30	100	300	300	600	30	100	300	300	600
TRG 2403										
3	34 ± 14		83 ± 11*			50 ± 16		180 ± 50*		
TRG 2404										
3	39 ± 4		81 ± 12*			82 ± 24		246 ± 75**		
TRG 2405										
64	**34 ± 12**		**87 ± 2***			**-13 ± 12**		**57 ± 28**		
77	52 ± 13*	*5 ± 7*	85 ± 13*			-14 ± 8	*9 ± 9*	68 ± 14		
156	30 ± 13	*12 ± 7*	48 ± 16			17 ± 23	*-5 ± 11*	43 ± 34		
190	70 ± 11*	*-6 ± 7*	83 ± 11*			25 ± 30	*13 ± 14*	109 ± 31**		
235	8 ± 7	*39 ± 7*	50 ± 9			-11 ± 13	*45 ± 18*	113 ± 15**		
238	19 ± 7	*73 ± 1**	84 ± 18*		*6 ± 28*	-17 ± 7	*151 ± 26***	118 ± 25**		*65 ± 15**

TABLE 4.

***IN VIVO* MELANOCORTIN RECEPTOR PROFILE**
In Vivo Cytokine Data for Compounds Received
90 or 105 Minutes

Array/ Compound #	% TNF-α Inhibition					% IL-10 Induction				
	IP			Oral		IP			Oral	
	30	100	300	300	600	30	100	300	300	600
239	13 ± 8	***10 ± 6***	66 ± 9*		***9 ± 14***	44 ± 35	***-29 ± 6***	197 ± 34**		***46 ± 14***
241	26 ± 15	***75 ± 3****	45 ± 9	38 ± 9*	74 ± 8*	117 ± 21	***310 ± 35*****	406 ± 46**	9 ± 23	77 ± 37*
242	21 ± 8	***60 ± 4****	68 ± 5*				***-9 ± 7***			
246	27 ± 9		80 ± 3*		-29 ± 31*					30 ± 5*
252	49 ± 14*		90 ± 2*		55 ± 13*	2 ± 13		307 ± 43*		69 ± 19*
253	***46 ± 8***		***80 ± 7***			***7 ± 21***		***325 ± 73*****		
262			83 ± 3*					191 ± 53*		
268	**-58 ± 18**		**9 ± 23**			**-3 ± 16**		**6 ± 17**		
TRG 2407										
39	24 ± 17		72 ± 5*			34 ± 13		366 ± 12**		
67	8 ± 14		73 ± 3*			-3 ± 15		29 ± 8		

TABLE 4.

IN VIVO MELANOCORTIN RECEPTOR PROFILE
In Vivo Cytokine Data for Compounds Received
90 or 105 Minutes

Array/ Compound #	% TNF-α Inhibition IP			% TNF-α Inhibition Oral		% IL-10 Induction IP			% IL-10 Induction Oral	
	30	100	300	300	600	30	100	300	300	600
TRG 2408										
30	30 ± 14		78 ± 3*	42 ± 14*	74 ± 4*	-20 ± 14		24 ± 12	33 ± 18	136 ± 41*
57	76 ± 8*	83 ± 2*	86 ± 2*	21 ± 11	72 ± 7*	123 ± 30	247 ± 75*	386 ± 25*	57 ± 11*	104 ± 16*
		87 ± 5*					225 ± 31*			
62	71 ± 6*		84 ± 8*	45 ± 11	35 ± 5	51 ± 15		270 ± 71*	43 ± 20	27 ± 10
TRG 2409										
2	57 ± 6*		65 ± 14	58 ± 2*	65 ± 2*	-30 ± 11		157 ± 57*	39 ± 15	82 ± 19*
14	31 ± 7		76 ± 7*	41 ± 9*	67 ± 4*	-27 ± 8		150 ± 50*	79 ± 29	193 ± 50*

Significantly different from saline ($^*p<0.05$, $^{**}p<0.01$)

italic values compounds tested at 105 minutes

Compounds originally chosen as negative controls based on single point binding data (10μM)

These results indicate that isoquinoline compounds can restrain LPS-induced cytokine activity.

EXAMPLE VII

Increasing Levels of IL-10 in Mice

This example describes the effectiveness of isoquinoline compounds in increasing the levels of IL-10 in mammals.

Table 4 shows the IL-10 inducing effect of various isoquinoline compounds in mouse plasma. Isoquinoline compounds were administered intraperitoneally to mice in doses of 30, 100 or 300 µg/mouse or orally in doses of 300 or 600 µg/mouse. Levels of IL-10 were measured 90 or 105 minutes after administration as indicated. Samples were collected and diluted, when appropriate, as described in Example VI. A 100 µl sample of plasma was assayed by ELISA for IL-10. Briefly, ELISA plates were coated with rat anti-mouse IL-10 monoclonal antibody (Pharmingen; San Diego CA). Samples or known concentrations of IL-10 were added to the coated plates and incubated for 2 hr at 37°C. Plates were washed and incubated with biotinylated rat anti-mouse IL-10 (R&D Systems; Minneapolis MN) for 1 hr at 37°C. Plates were washed and incubated with streptavidin-HRP 30 min at 37°C, and HRP activity was detected with hydrogen peroxide and TMB using standard immunoassay procedures.

Table 4 shows a dose dependent increase in IL 10 levels up to 400% greater than control mice administered saline. Oral administration also caused a significant increase in IL-10 of up to 200%. TRG 2408-30

is particularly effective at increasing IL-10 when administered orally.

These results demonstrate that isoquinoline compounds can significantly increase the levels of IL-10.

EXAMPLE VIII

Effect of Isoquinoline Compounds on Arachidonic Acid Induced Dermal Inflammation

This example describes the effect of isoquinoline compounds on arachidonic acid induced dermal inflammation.

Female BALB/c mice (17-22 g) were used and administered the test isoquinoline compounds or positive control compounds 30 to 60 min prior to topical application of arachidonic acid. Indomethacin and HP 228 were used as positive controls. Compounds were administered orally (p.o.) or intraperitoneally (i.p.). Initial ear thickness (left and right) was measured using spring loaded micro-calipers. Arachidonic acid was applied to mice anesthetized with a cocktail of ketamine/xylazine (7.0 mg/ml and 0.6 mg/ml, respectively) administered i.p. (300 µl/mouse). Utilizing a micro-pipette, 20 µl of arachidonic acid solution (100 mg/ml ethanol or acetone) was applied to the right ear (10 µl to inner and 10 µl to outer surfaces of both ears for a total of 2 mg arachidonic acid per right ear), and 20 µl of vehicle (ethanol or acetone) was applied to the left ear. Mice were returned to their cages to recover. Mice were again anesthetized 50 min after arachidonic acid application and their ears measured.

Dermal inflammation was determined by subtracting the difference of the vehicle treated left ear (L_{60}-L_0) from the difference of the arachidonic acid treated right ear (R_{60}-R_0). Ear thickness measurements were averaged for each group, and the responses in the vehicle treated control group (*Cr;* saline or PBS) were subtracted from the response noted in the isoquinoline compound treated group (Tr) to give the relative inflammatory response for each treatment group compared to the control group. The percent inhibition is defined by the equation: % inhibition = $(Cr - Tr)/(Cr) \times 100$.

Figure 2 shows inhibition of arachidonic acid induced dermal inflammation with TRG 2405-241 (600 µg/mouse) comparable to that seen with indomethacin (1 mg/mouse) administered orally. Figure 3 shows inhibition of arachidonic acid induced dermal inflammation with TRG 2405-241 (300 µg/mouse) comparable to that seen with with HP 228 (100 µg/mouse) administered intraperitoneally. Figure 4 shows inhibition of arachidonic acid induced dermal inflammation with HP 228, TRG 2405-190, TRG 2405-241, TRG 2405-252 or TRG 2405-253 (100 µg/mouse) administered intraperitoneally. As shown in Figure 5, TRG 2409-2 showed a dose dependent reduction in the level of arachidonic acid-induced dermal inflammation, comparable to the reduction seen with HP 228. TRG 2409-14 decreased dermal inflammation to a lesser extent than TRG 2409-2.

These results show that isoquinoline compounds significantly reduce arachidonic acid-induced dermal inflammation.

EXAMPLE IX

Reduction in Body Weight Due to Administration of Isoquinoline Compounds

This example demonstrates that administration of an isoquinoline compound can cause a decrease in the body weight of a subject.

Adult male Sprague-Dawley rats (175-225 g) were used to assess the effect of isoquinoline compounds on food uptake and body weight. Baseline body weight and food consumption measurements were taken for 3 days prior to start of the study (Day 0). On Day -1, the food was taken away from the animals at 5:00 PM. The next morning (Day 0), body weight measurements were taken, and the animals were divided into treatment groups with 6 animals in each group. The treatment groups were saline control, HP 228 positive control and test isoquinoline compounds. Saline was administered i.p. at 1 ml/kg. HP 228 and test isoquinoline compounds were administered i.p. at 5 mg/kg. The injections were initiated at 2:00 PM on Day 0.

Body weight and food consumption measurements were taken at 9 hr (Day 0; 11:00 PM) and at 18 hr (Day 1, 8:00 AM) after injection. At the end of the study, all evaluated parameters (9 and 18 hour body weight and food consumption) were analyzed by standard statistical methods. Significance ($P<0.05$) was determined by one-way ANOVA, ANOVA for repeated measures, or Student's t-test.

Administration of TRG 2405-190 or TRG 2405-241 caused a significant decrease in the weight gain and food consumption of rats at 18 hours after injection (see Figure 6). The level of reduction was similar to that seen with HP 228. These results indicate that an

isoquinoline compound can decrease weight gain and food intake in subjects. Figure 7 shows that significant differences in body weight and food consumption relative to control could be observed at 9 hours as well as 18 hours in rats treated with TRG 2405-252 or TRG 2405-253.

These results indicate that a cytokine regulatory agent is useful for decreasing the body weight of a subject.

EXAMPLE X

Penile Erection Due to Administration of Isoquinoline Compound

Assay Method

Adult male rats were housed 2-3 per cage and were acclimated to the standard vivarium light cycle (12 hr. light, 12 hr. dark), rat chow and water for a least a week prior to testing. All experiments were performed between 9 a.m. and noon and rats were placed in cylindrical, clear plexiglass chambers during the 60 minute observation period. Mirrors were positioned below and to the sides of the chambers, to improve viewing.

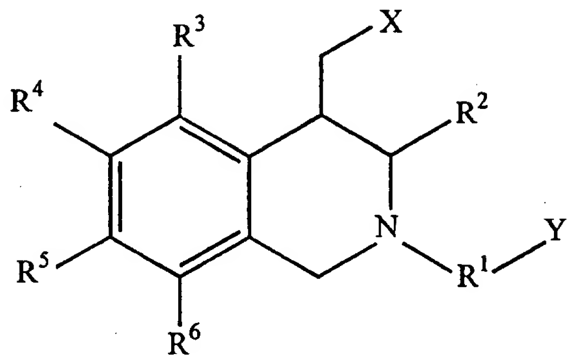
Observations began 10 minutes after an unstraperitoneal injection of either saline or compound. An observer counted the number of grooming motions, stretches, yawns and penile erections (spontaneously occurring, not elicited by genital grooming) and recorder them every 5 minutes, for a total of 60 minutes (see Figures 8 and 9). The observer was unaware of the treatment and animals were tested once, with n=6 in each group. Values in the figures represent the group mean

positive control for penile erections. Significant differences between groups were determined by an overall analysis of variance and the Student Neunmann-Keuls post hoc test was used to identify individual differences between groups ($p \leq 0.05$).

Although the invention has been described with reference to the examples provided above, it should be understood that various modifications can be made without departing from the spirit of the invention. Accordingly, the invention is limited only by the following claims.

We claim:

1. An isoquinoline compound of the formula:



wherein:

R^1 is selected from the group consisting of C_1 to C_9 alkylene, C_1 to C_9 substituted alkylene, C_2 to C_9 alkenylene, C_2 to C_9 substituted alkenylene, C_2 to C_9 alkynylene, C_2 to C_9 substituted alkynylene, C_7 to C_{12} phenylalkylene, C_7 to C_{12} substituted phenylalkylene and a group of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

wherein u is selected from a number 1 to 8; and R^8 is selected from the group consisting of a hydrogen atom, C_1 to C_9 alkyl, C_1 to C_9 substituted alkyl, C_7 to C_{12} phenylalkyl and C_7 to C_{12} substituted phenylalkyl;

R^2 is selected from the group consisting of phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{12} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, a heterocyclic ring and a substituted heterocyclic ring;

R^3, R^4, R^5 and R^6 are, independently, a hydrogen atom, halo, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_2 to C_7 alkenyl, C_2 to C_7 alkynyl, C_1 to C_6 substituted alkyl, C_2 to C_7 substituted alkenyl, C_2 to C_7 substituted alkynyl, C_1 to C_7 alkoxy, C_1 to C_7 acyloxy, C_1 to C_7 acyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, a heterocyclic ring, C_7 to C_{12} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, cyclic C_2 to C_7 alkylene, substituted cyclic C_2 to C_7 alkylene, cyclic C_2 to C_7 heteroalkylene, substituted cyclic C_2 to C_7 heteroalkylene, carboxy, protected carboxy, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, C_1 to C_4 alkylthio, C_1 to C_4 alkylsulfonyl, C_1 to C_4 alkylsulfoxide, phenylthio, substituted phenylthio, phenylsulfoxide, substituted phenylsulfoxide, phenylsulfonyl and substituted phenylsulfonyl;

X is selected from the group consisting of hydroxy, amino, protected amino, (monosubstituted)amino, (disubstituted)amino, an amino acid, aniline, substituted aniline, a heterocyclic ring, an

aminosubstituted heterocyclic ring, and a substituted aminosubstituted heterocyclic ring; and

Y is selected from the group consisting of CH_2NHR^7 and $C(O)NHR^7$, wherein R^7 is a hydrogen atom, C_1 to C_6 alkyl and C_1 to C_6 substituted alkyl.

2. The isoquinoline compound of claim 1, wherein:

R^1 is selected from the group consisting of C_1 to C_9 alkylene, C_1 to C_9 substituted alkylene and a group of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

wherein u is selected from a number 1 to 8; and R^8 is selected from the group consisting of a hydrogen atom, C_1 to C_9 alkyl, C_1 to C_9 substituted alkyl, C_7 to C_{12} phenylalkyl and C_7 to C_{12} substituted phenylalkyl.

3. The isoquinoline compound of claim 1, wherein:

R^2 is selected from the group consisting of phenyl, substituted phenyl, a heterocyclic ring, amino substituted heterocyclic ring and a substituted heterocyclic ring.

4. The isoquinoline compound of claim 1, wherein:

R^3, R^4, R^5 and R^6 are, independently, a hydrogen atom.

5. The isoquinoline compound of claim 1, wherein:

X is selected from the group consisting of hydroxy, amino, protected amino, (monosubstituted)amino, (disubstituted)amino, aniline, substituted aniline, a heterocyclic ring, a substituted heterocyclic ring, an aminosubstituted heterocyclic ring, and a substituted aminosubstituted heterocyclic ring.

6. The isoquinoline compound of claim 1, wherein:

Y is CH_2NHR^7, wherein R^7 is selected from the group consisting of a hydrogen atom, C_1 to C_6 alkyl and C_1 to C_6 substituted alkyl.

7. The isoquinoline compound of claim 1, wherein:

R^1 is selected from the group consisting of C_1 to C_9 alkylene, C_1 to C_9 substituted alkylene and a group of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

wherein u is selected from a number 1 to 8; and R^8 is selected from the group consisting of a hydrogen atom, C_1 to C_9 alkyl, C_1 to C_9 substituted alkyl, C_7 to C_{12} phenylalkyl and C_7 to C_{12} substituted phenylalkyl;

R^2 is selected from the group consisting of phenyl, substituted phenyl, a heterocyclic ring, amino substituted heterocyclic ring and a substituted heterocyclic ring;

R^3, R^4, R^5 and R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of hydroxy, amino, protected amino, (monosubstituted)amino, (disubstituted)amino, aniline, substituted aniline, a heterocyclic ring, a substituted heterocyclic ring, an aminosubstituted heterocyclic ring, and a substituted aminosubstituted heterocyclic ring; and

Y is CH_2NHR^7, wherein R^7 is selected from the group consisting of a hydrogen atom, C_1 to C_6 alkyl and C_1 to C_6 substituted alkyl.

8. The isoquinoline compound of claim 1, wherein:

R^1 is selected from the group consisting of methylene and a group of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in either chiral form wherein u is selected from a number 1 to 4; and R^8 is selected from the group consisting of methyl, ethyl, phenethyl, 2-(N-methyl)aminoethyl, 2-aminoethyl, 2-(N-methyl)aminopropyl, hydroxyethyl, 2-(N-methyl)amino-2-phenethyl, a reduced and/or modified form of succinic anhydride, methoxyethyl, butyl, cyclohexanemethyl, benzyl, 4-bromophenethyl, 4-methoxyphenethyl, 4-chlorobenzyl, 4-methoxybenzyl, 2-naphthylethyl and cyclohexylethyl;

R^2 is selected from the group consisting of phenyl, 2-hydroxyphenyl, 1,4-benzodioxan-6-yl, 1-methyl-2-pyrrolyl, 1-naphthyl, 2,3,4-trifluorophenyl, 2,3,5-trichlorophenyl,

2,3-(methylenedioxy)phenyl, 2,3-difluorophenyl, 2,4-dichlorophenyl, 2,6-difluorophenyl, 2-bromophenyl, 2-chloro-5-nitrophenyl, 2-chloro-6-fluorophenyl, 2-aminomethylphenyl, 2-fluorophenyl, 2-imidazolyl, 2-methoxybenzyl, 2-naphthyl, 2-thiophene-yl, 3,4-(methylenedioxy)phenyl, 3,4-dihydroxyphenyl, 3,4-dichlorophenyl, 3,4-difluorophenyl, 3,5-bis(trifluoromethyl)phenyl, 3,5-dihydroxyphenyl, 3,5-dichlorophenyl, 3,5-dimethoxyphenyl, 3,5-dimethyl-4-hydroxyphenyl, 3-(3,4-dichlorophenoxy)phenyl, 3-(4-methoxyphenoxy)phenyl, 3-(trifluoromethyl)phenyl, 3-bromo-4-fluorophenyl, 3-bromophenyl, 3-hydroxymethylphenyl, 3-aminomethylphenyl, 3-fluoro-4-methoxyphenyl, 3-fluorophenyl, 3-hydroxyphenyl, 3-methoxy-4-hydroxy-5-nitrophenyl, 3-methoxyphenyl, 3-methyl-4-methoxyphenyl, 3-methylphenyl, 3-nitro-4-chlorophenyl, 3-nitrophenyl, 3-phenoxyphenyl, 3-pyridinyl, 3-thiophene-yl, 4-(3-dimethylaminopropoxy)phenyl, 4-(dimethylamino)phenyl, 4-hydroxymethylphenyl, 4-(methylthio)phenyl, 4-(trifluoromethyl)phenyl, 4-ethylaminophenyl, 4-methoxyphenyl (p-anisaldehyde), 4-biphenylcarboxaldehyde, 4-bromophenyl, 4-aminomethylphenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-isopropylphenyl, 4-methoxy-1-naphthaldehyde, 4-methylphenyl, 3-hydroxy-4-nitrophenyl, 4-nitrophenyl, 4-phenoxyphenyl, 4-propoxyphenyl, 4-pyridinyl, 3-methoxy-4-hydroxy-5-bromophenyl, 5-methyl-2-thiophene-yl, 5-methyl-2-furyl, 8-hydroxyquinoline-2-yl, 9-ethyl-3-carbazole-yl, 9-formyl-8-hydroxyjulolidin-yl, pyrrole-2-yl,

3-hydroxy-4-methoxyphenyl, 4-methylsulphonylphenyl, 4-methoxy-3-(sulfonic acid, Na)phenyl, 5-bromo-2-furyl, 4-ethoxyphenyl, 4-propoxyphenyl, 4-butoxyphenyl, 4-amylphenyl, 4-propylaminophenyl, 4-butylaminophenyl, 4-pentylaminophenyl, 4-cyclohexylmethylaminophenyl, 4-isobutylaminophenyl, 4-(2-methoxy)-ethylaminophenyl, 4-methoxybenzylaminophenyl, phenethylaminophenyl, 4-methoxyphenethylaminophenyl, 2-(2-norbornyl)-ethylaminophenyl, 3,4-dichlorphenethylaminophenyl, 4-benzylaminophenyl and 4-p-chlorobenzylaminophenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of anilinyl, N-methylanilinyl, 2-chloroanilinyl, 2-methoxyanilinyl, 3-chloroanilinyl, 3-ethoxyanilinyl, 3-aminophenol, 4-chloroanilinyl, 4-methoxyanilinyl, benzylamino, N-benzylmethylamino, 2-chlorobenzylamino, 2-(trifluoromethyl)benzylamino, 2-hydroxybenzylamino, 3-methoxybenzylamino, 3-(trifluoromethyl)benzylamino, 4-chlorobenzylamino, 4-methoxybenzylamino, 4-(trifluoromethyl)benzylamino, phenethylamino, 2-chlorophenethylamino, 2-methoxyphenethylamino, 3-chlorophenethylamino, 4-methoxyphenthylamino, 3-phenyl-1-propylamino, cyclopentylamino, isopropylamino, cycloheptylamino, N-methylcyclohexylamino, (aminomethyl)cyclohexane, piperidinyl, morpholinyl, 1-aminopiperidinyl, diethylamino, 3-hydroxypropyl, isopropylamino,

(2-aminoethyl)-trimethylaminoethyl chloride, ammonia and hydroxy; and

Y is CH_2NH_2.

9. The isoquinoline compound of claim 1, wherein:

R^1 is selected from the group consisting of methylene and a group of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in either chiral form wherein u is selected from a number 1, 2 and 4 and R^8 is methyl;

R^2 is selected from the group consisting of phenyl, 2-hydroxyphenyl, 1,4-benzodioxan-6-yl, 1-methyl-2-pyrrolyl, 1-naphthyl, 2,3,4-trifluorophenyl, 2,3,5-trichlorophenyl, 2,3-(methylenedioxy)phenyl, 2,3-difluorophenyl, 2,4-dichlorophenyl, 2,6-difluorophenyl, 2-bromophenyl, 2-chloro-5-nitrophenyl, 2-chloro-6-fluorophenyl, 2-cyanophenyl, 2-fluorophenyl, 2-imidazolyl, 2-methoxybenzyl, 2-naphthyl, 2-thiophene-yl, 3,4-(methylenedioxy)phenyl, 3,4-dihydroxyphenyl, 3,4-dichlorophenyl, 3,4-difluorophenyl, 3,5-bis(trifluoromethyl)phenyl, 3,5-dihydroxyphenyl, 3,5-dichlorophenyl, 3,5-dimethoxyphenyl, 3,5-dimethyl-4-hydroxyphenyl, 3-(3,4-dichlorophenoxy)phenyl, 3-(4-methoxyphenoxy)phenyl, 3-(trifluoromethyl)phenyl, 3-bromo-4-fluorophenyl, 3-bromophenyl, 3-hydroxymethylphenyl,

3-aminomethylphenyl, 3-fluoro-4-methoxyphenyl, 3-fluorophenyl, 3-hydroxyphenyl, 3-methoxy-4-hydroxy-5-nitrophenyl, 3-methoxyphenyl, 3-methyl-4-methoxyphenyl, 3-methylphenyl, 3-nitro-4-chlorophenyl, 3-nitrophenyl, 3-phenoxyphenyl, 3-pyridinyl, 3-thiophene-yl, 4-(3-dimethylaminopropoxy)phenyl, 4-(dimethylamino)phenyl, 4-hydroxymethylphenyl, 4-(methylthio)phenyl, 4-(trifluoromethyl)phenyl, 4-ethylaminophenyl, 4-methoxyphenyl, 4-biphenyl, 4-bromophenyl, 4-aminomethylphenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-isopropylphenyl, 4-methoxy-1-naphthyl, 4-methylphenyl, 3-hydroxy-4-nitrophenyl, 4-nitrophenyl, 4-phenoxyphenyl, 4-propoxyphenyl, 4-pyridinyl, 3-methoxy-4-hydroxy-5-bromophenyl, 5-methyl-2-thiophene-yl, 5-methyl-2-furyl, 8-hydroxyquinoline-2-yl, 9-ethyl-3-carbazole-yl, 9-formyl-8-hydroxyjulolidin-yl, pyrrole-2-yl, 3-hydroxy-4-methoxyphenyl, 4-methylsulphonylphenyl, 4-methoxy-3-(sulfonic acid, Na)phenyl and 5-bromo-2-furyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is cyclohexylamino; and

Y is CH_2NH_2.

10. The isoquinoline compound of claim 1, wherein:

R^1 is selected from the group consisting of methylene and a group of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in either chiral form wherein u is selected from a number 1, 2 and 4 and R^8 is methyl;

R^2 is selected from the group consisting of 3-(3,4-dichlorophenoxy)phenyl, 1-methyl-2-pyrrolyl, 3-phenoxyphenyl, 4-phenoxyphenyl, 3-methoxy-4-hydroxy-5-bromophenyl and 9-ethyl-3-carbazolyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is 2-hydroxybenzyl; and

Y is CH_2NH_2.

11. The isoquinoline compound of claim 1, wherein:

R^1 is selected from the group consisting of methylene and a group of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in either chiral form wherein u is selected from a number 1, 2 and 4 and R^8 is methyl;

R^2 is selected from the group consisting of 2,4-dichlorophenyl, 4-biphenyl and 4-ethylaminophenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of anilinyl, N-methylanilinyl, 2-chloroanilinyl, 2-methoxyanilinyl, 3-chloroanilinyl, 3-ethoxyanilinyl, 3-aminophenol, 4-chloroanilinyl, 4-methoxyanilinyl, benzylamino,

N-benzylmethylamino, 2-chlorobenzylamino, 2-(trifluoromethyl)benzylamino, 2-hydroxybenzylamino, 3-methoxybenzylamino, 3-(trifluoromethyl)benzylamino, 4-chlorobenzylamino, 4-methoxybenzylamino, 4-(trifluoromethyl)benzylamino, phenethylamino, 2-chlorophenethylamino, 2-methoxyphenethylamino, 3-chlorophenethylamino, 4-methoxyphenthylamino, 3-phenyl-1-propylamino, cyclopentylamino, isopropylamino, cycloheptylamino, N-methylcyclohexylamino, cyclohexylmethylamino, piperidinyl, morpholinyl, 1-aminopiperidinyl, diethylamino, allylamino, isopropylamino, (2-aminoethyl)-trimethylammonium, ammonium and hydroxy; and

Y is CH_2NH_2.

12. The isoquinoline compound of claim 1, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in either chiral form wherein u is selected from a number 1, 2 and 4 and R^8 is selected from the group consisting of a hydrogen atom, methyl, phenylethyl, 2-(N-methyl)aminoethyl and 2-aminoethyl;

R^2 is selected from the group consisting of 2,4-dichlorophenyl, 4-biphenyl and 4-ethylaminophenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of cyclohexylamino and 2-hydroxybenzylamino; and

Y is CH_2NH_2.

13. The isoquinoline compound of claim 1, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in the (s) chiral form wherein u is the number 4 and R^8 is methyl;

R^2 is selected from the group consisting of 4-propylaminophenyl, 4-butylaminophenyl, 4-cyclohexylmethylaminophenyl, 4-isobutylaminophenyl, 4-(2-methoxy)-ethylaminophenyl, 4-(4-methoxybenzyl)aminophenyl, 4-phenethylaminophenyl, 4-(4-methoxyphenethyl)aminophenyl, 2-(2-norboranyl)-ethylaminophenyl, 3,4-dichlorphenethylaminophenyl, 4-benzylaminophenyl and 4-p-chlorobenzylaminophenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of cyclohexylamino and 2-hydroxybenzylamino; and

Y is CH_2NH_2.

14. The isoquinoline compound of claim 1, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in the (s) chiral form wherein u is selected from the numbers 3 and 4 and R^8 is selected from the group consisting of a hydrogen atom, methyl, ethyl, phenylethyl, 2-(N-methyl)aminoethyl, 2-aminoethyl, 2-(N-methyl)propyl, hydroxyethyl, 2-(N-methyl)amino-2-phenethyl, a reduced form of succinic anhydride, methoxyethyl, butyl, cyclohexylmethyl, benzyl, 4-bromophenethyl, 4-methoxyphenethyl, 4-chlorobenzyl, 4-methoxybenzyl, 2-naphthylethyl and cyclohexylethyl;

R^2 is selected from the group consisting of 4-biphenyl, 4-ethylaminophenyl and 4-butylaminophenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is selected from the group of cyclohexylamino, ammonia and phenethylamino; and

Y is CH_2NH_2.

15. The isoquinoline compound of claim 1, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in the (s) chiral form wherein u is selected from the numbers 3 and 4 and R^8 is selected from the group consisting of methyl, phenethyl and benzyl;

R^2 is selected from the group consisting of 4-pentylaminophenyl, 4-ethoxyphenyl, 4-propoxyphenyl, 4-butoxyphenyl and 4-amylphenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is phenethylamino; and

Y is CH_2NH_2.

16. The isoquinoline compound of claim 1, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in the (r) chiral form wherein u is selected from the numbers 3 and 4 and R^8 is selected from the group consisting of methyl, 2-(N-methyl)aminoethyl, 2-aminoethyl and phenethyl;

R^2 is selected from the group consisting of 4-biphenyl, 4-ethylaminophenyl and 4-nitrophenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of phenethyl, ammonia and cyclohexylamino; and

Y is CH_2NH_2.

17. The isoquinoline compound of claim 1, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in the (s) chiral form wherein u is 3 and R^8 is selected from the group consisting of a hydrogen atom, phenylethyl, benzyl and 4-isobutyl-α-methylphenylethyl;

R^2 is selected from the group consisting of 2,4-dichlorophenyl, 2-bromophenyl, 3,5-bis(trifluoromethyl)phenyl, 3-phenoxyphenyl, 4-phenoxyphenyl and 4-propoxyphenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of 2-(trifluoromethyl)benzylamino, 2-ethoxybenzylamino, 2-methoxyphenethylamino, 3-chlorophenethylamino, 3-methoxybenzylamino, 4-methoxybenzylamino, 4-methoxyphenethylamino, benzylamino, cycloheptylamino and cyclohexylamino; and

Y is CH_2NH_2.

18. The isoquinoline compound of claim 1, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in the (s) chiral form wherein u is selected from the numbers 3 and 4 and R^8 is selected from the group consisting of ethyl and cyclohexylethyl;

R^2 is selected from the group consisting of 4-amylphenyl, 4-butoxyphenyl, 4-butylaminophenyl, 4-ethoxyphenyl, 4-ethylphenyl and 4-n-propoxyphenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of ammonia, hydroxy and phenethylamino; and

Y is CH_2NH_2.

19. The isoquinoline compound of claim 1, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in the (s) chiral form wherein u is 3 and R^8 is selected from the group consisting of 4-(amino)-butyl, 4-(aminobenzyl)-butyl, 4-(diethylamino)-butyl, 4-(isopropylamino)-butyl, 4-(hydroxy)-butyl, 4-(phenethylamino)-butyl,

4-(piperidino)-butyl, 4-(t-butylamino)-butyl and 4-(aminophenyl)-butyl;

R^2 is 4-ethylaminophenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of ammonia and phenethylamino; and

Y is CH_2NH_2.

20. The isoquinoline compound of claim 1, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in the (s) chiral form wherein u is 3 and R^8 is selected from the group consisting of
4-(isopropylamino)-butyl, 4-(benzoamino)-butyl,
4-(diethylamino)-butyl, 4-(phenethylamino)-butyl,
5-(isopropylamino)-(3,4)cyclopropane-pentyl,
5-(benzoamino)-(3,4)cyclopropane-pentyl,
5-(diethylamino)-(3,4)cyclopropane-pentyl,
5-(phenethylamino)-(3,4)cyclopropane-pentyl,
2-amino-2-ethoxy-N-ethylisopropylamino-
2-amino-2-ethoxy-N-ethylbenzyl,
2-amino-2-ethoxy-N-ethyldiethyl,
2-amino-2-ethoxy-N-ethylphenethyl,
(2,3)benzyl-4-isopropylamino,
(2,3)benzyl-4-benzylamino,
(2,3)benzyl-4-diethylamino,
(2,3)benzyl-4-phenethylamino,

3-(hydroxy)-5-(isopropylamino)-3-pentyl,
3-(hydroxy)-5-(benzylamino)-3-pentyl,
3-(hydroxy)-5-(diethylamino)-3-pentyl and
3-(hydroxy)-5-(phenethylamino)-3-pentyl;

R^2 is 4-ethylaminophenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is slected from the group consisting of phenethylamino and ammonia; and

Y is CH_2NH_2.

21. The isoquinoline compound of claim 1, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in the (s) chiral form wherein u is 4 and R^8 is selected from the group consisting of benzyl, p-methylbenzyl, p-bromobenzyl, p-methoxybenzyl and 4-phenylbenzyl;

R^2 is selected from the group consisting of 3,5-bis(trifluoromethyl)phenyl and 3-(trifluoromethyl)phenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of phenethylamino, tyramino,

2-(4-methoxyphenyl)ethylamino, 3,4-dimethoxyphenylethylamino, 4-ethoxyphenethylamino, 4-phenoxyphenethylamino, 2-(4-chlorophenyl)ethylamino and 2-(3-methoxyphenyl)ethylamino; and

Y is CH_2NH_2.

22. The isoquinoline compound of claim 1, wherein:

R^1 is 5-(2-aminoethylamino)pentyl;

R^2 is p-(N-ethylamino)benzyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of 2-methoxybenzylamino, 4-methoxybenzylamino, cyclohexylamino, phenethylamino and ammonia; and

Y is CH_2NH_2.

23. The isoquinoline compound of claim 1, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in the (s) chiral form wherein u is selected from the numbers 3 and 4 and R^8 is selected from the group consisting of pentyl, 4-phenoxybutyl and 4-hydroxypentyl;

R^2 is p-(N-ethylamino)benzyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of phenethylamino and ammonia; and

Y is CH_2NH_2.

24. The isoquinoline compound of claim 1, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in the (s) chiral form wherein u is 4 and R^8 is selected from the group consisting of (α,α,α-trifluoro-p-tolyl)ethyl, 3-(4-methoxyphenyl)propyl, 4-biphenylmethyl, 4-biphenylethyl, 4-chlorophenylethyl, 4-phenoxybutyl, butyl, glycolyl, a hydrogen atom, hydrocinnamylmethyl, isobutylmethyl, methyl, p-methoxybenzyl, 4-hydroxybutyl and 2-(trimethyl)ethyl;

R^2 is selected from the group consisting of 4-propoxyphenyl, 4-amylphenyl and 3,5-bistrifluoromethylphenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of ammonia and cycloheptylamino; and

Y is CH_2NH_2.

25. The isoquinoline compound of claim 1, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in the (s) chiral form wherein u is 4 and R^8 is selected from the group consisting of methyl and phenethyl;

R^2 is selected from the group consisting of 4-propoxyphenyl, 4-amylphenyl and 3,5-bistrifluoromethylphenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of 4-chlorobenzylamino, 4-methoxybenzylamino, 4-methoxyphenethylamino, phenylamino, benzylamino, cyclohexanemethylamino, cyclohexylamino, cyclooctylamino, cyclopentylamino, diethylamino, ethanolamino, isopropylamino, morpholino, n-methylanilino, n-methylcyclohexylamino, hydroxy, p-anisidino, phenethylamino, piperidino and t-butylamino; and

Y is CH_2NH_2.

26. The isoquinoline compound of claim 1, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in the (s) chiral form wherein u is 4 and R^8 is selected from the group consisting of (α,α,α-trifluoro-p-tolyl)ethyl, 1-adamantaneethyl, 3-(4-methoxyphenyl)propyl, 4-phenylbenzyl, 4-phenylphenethyl, 4-chlorophenethyl, 4-imidazolemethyl, 4-methoxyphenyethyl, 4-phenoxypentyl, α,α,α-trifluoro-p-toluylethyl, ethyl, benzyl, butyl, glycolyl, hydrocinnamylmethyl, isobutylmethyl, p-methoxybenzyl, phenethyl, 4-hydroxybutyl and 2-(trimethyl)ethyl;

R^2 is selected from the group consisting of 4-propoxyphenyl, 4-amylphenyl and 3,5-bistrifluoromethylphenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of ammonia and cycloheptylamino; and

Y is CH_2NH_2.

27. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is methyl; R^2 is 2,4-dichlorophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2.

28. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is methyl; R^2 is 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2.

29. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is methyl; R^2 is 4-biphenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2.

30. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is methyl; R^2 is 4-phenoxyphenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2.

31. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is methyl; R^2 is 4-propoxyphenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2.

32. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is methyl; R^2 is 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2.

33. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 3; and R^8 is 2-phenylethyl; R^2 is 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is 2-hydroxybenzylamino; and Y is CH_2NH_2.

34. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 3; and R^8 is 2-phenylethyl; R^2 is 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2.

35. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is methyl; R^2 is 4-butylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is 2-hydroxybenzylamino; and Y is CH_2NH_2.

36. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is methyl; R^2 is 4-butylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2.

37. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is 2-(N-methyl)ethyl; R^2 is 4-biphenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is amino; and Y is CH_2NH_2.

38. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is butyl; R^2 is 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2.

39. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is ethyl; R^2 is 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is amino; and Y is CH_2NH_2.

40. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is 2-cyclohexylethyl; R^2 is 4-butylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is amino; and Y is CH_2NH_2.

41. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 3; and R^8 is 2-cyclohexylethyl; R^2 is 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is amino; and Y is CH_2NH_2.

42. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 3; and R^8 is 4-hydroxybutyl; R^2 is 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is 2-phenethylamino; and Y is CH_2NH_2.

43. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is 2-phenethyl; R^2 is 4-propoxyphenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is cycloheptylamino; and Y is CH_2NH_2.

44. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is ethyl; R^2 is 4-ethoxyphenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is amino; and Y is CH_2NH_2.

45. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is ethyl; R^2 is 4-propoxyphenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is amino; and Y is CH_2NH_2.

46. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is ethyl; R^2 is 4-n-butoxyphenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is amino; and Y is CH_2NH_2.

47. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is ethyl; R^2 is 4-n-pentylphenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is amino; and Y is CH_2NH_2.

48. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 3; and R^8 is 4-hydroxybutyl; R^2 is 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are,

independently, a hydrogen atom; X is amino; and Y is CH_2NH_2.

49. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 3; and R^8 is pentyl; R^2 is 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is 2-phenethylamino; and Y is CH_2NH_2.

50. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is 4-hydroxybutyl; R^2 is 4-pentylphenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is amino; and Y is CH_2NH_2.

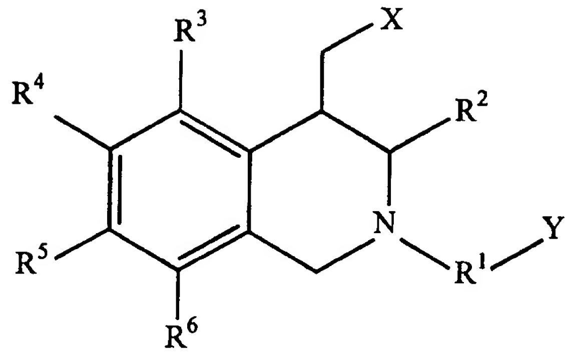
51. A method of altering the activity of a melanocortin receptor in a subject, comprising administering to the subject an effective amount of a melanocortin receptor ligand, wherein said melanocortin receptor ligand comprises the isoquinoline compound of claim 1.

52. The method of claim 51, wherein said melanocortin receptor activity regulates the activity of a cytokine.

53. The method of claim 52, wherein said melanocortin receptor ligand decreases said cytokine activity.

54. The method of claim 53, wherein said cytokine activity is tumor necrosis factor-α activity.

55. The method of claim 54, wherein said melanocortin receptor ligand comprises an isoquinoline compound of the formula:



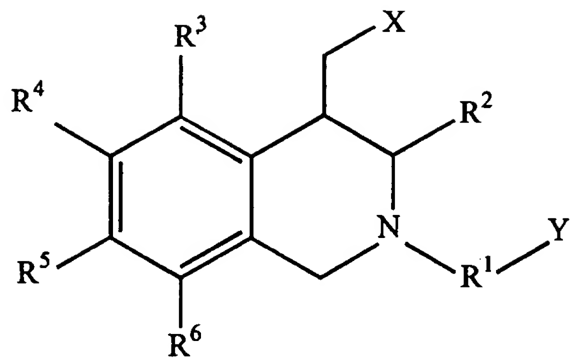
wherein:

R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is methyl; R^2 is selected from the group consisting of 2,4-dichlorophenyl, 4-biphenyl, 4-phenoxyphenyl, 4-propoxyphenyl and 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2.

56. The method of claim 52, wherein said melanocortin receptor ligand enhances said cytokine activity.

57. The method of claim 56, wherein said cytokine activity is interleukin-10 activity.

58. The method of claim 57, wherein said melanocortin receptor ligand comprises an isoquinoline compound of the formula:

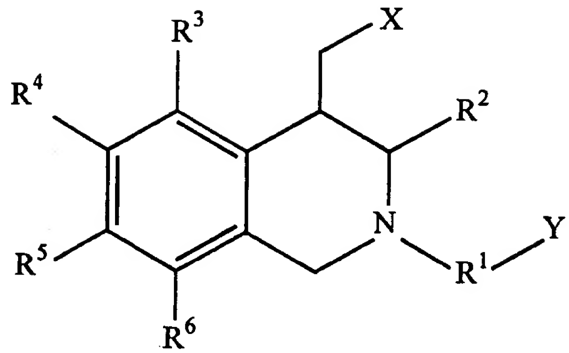


wherein:

R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is methyl; R^2 is selected from the group consisting of 2,4-dichlorophenyl, 4-biphenyl, 4-phenoxyphenyl, 4-propoxyphenyl and 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2.

59. A method of decreasing inflammation in a subject, comprising administering to the subject an effective amount of a melanocortin receptor ligand, wherein said melanocortin receptor ligand comprises the isoquinoline compound of claim 1.

60. The method of claim 59, wherein said melanocortin receptor ligand comprises an isoquinoline compound of the formula:

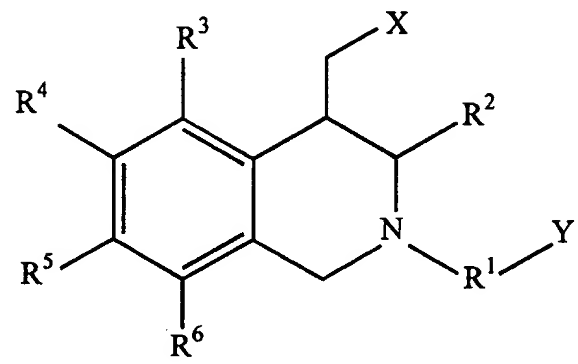


wherein:

R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is methyl; R^2 is selected from the group consisting of 2,4-dichlorophenyl, 4-biphenyl, 4-phenoxyphenyl, 4-propoxyphenyl and 4-butylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X selected from the group consisting of cyclohexylamino and 2-hydroxybenzylamino; and Y is CH_2NH_2.

61. A method of decreasing the body weight of a subject, comprising administering to the subject an effective amount of a melanocortin receptor ligand, wherein said melanocortin receptor ligand comprises the isoquinoline compound of claim 1.

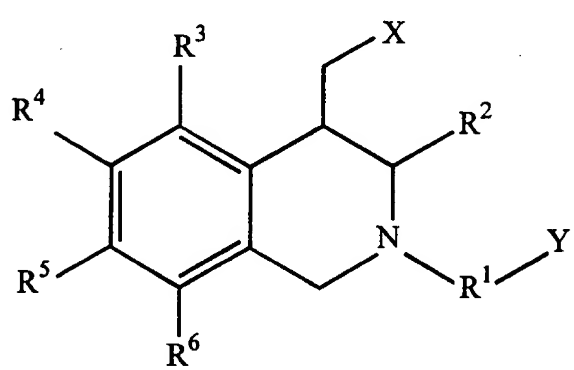
62. The method of claim 61, wherein said melanocortin receptor ligand comprises an isoquinoline compound of the formula:



wherein:

R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is methyl; R^2 is selected from the group consisting of 2,4-dichlorophenyl, 4-biphenyl, 4-phenoxyphenyl and 4-propoxyphenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2.

63. A combinatroial library comprising two or more isoquinoline compounds of the formula:



wherein:

R^1 is selected from the group consisting of C_1 to C_9 alkylene, C_1 to C_9 substituted alkylene, C_2 to C_9 alkenylene, C_2 to C_9 substituted alkenylene, C_2 to C_9 alkynylene, C_2 to C_9 substituted alkynylene, C_7 to C_{12} phenylalkylene, C_7 to C_{12} substituted phenylalkylene and a group of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

wherein u is selected from a number 1 to 8; and R^8 is selected from the group consisting of a hydrogen atom, C_1 to C_9 alkyl, C_1 to C_9 substituted alkyl, C_7 to C_{12} phenylalkyl and C_7 to C_{12} substituted phenylalkyl;

R^2 is selected from the group consisting of phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{12} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, a heterocyclic ring and a substituted heterocyclic ring;

R^3, R^4, R^5 and R^6 are, independently, a hydrogen atom, halo, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_2 to C_7 alkenyl, C_2 to C_7 alkynyl, C_1 to C_6 substituted alkyl, C_2 to C_7 substituted alkenyl, C_2 to C_7 substituted alkynyl, C_1 to C_7 alkoxy, C_1 to C_7 acyloxy, C_1 to C_7 acyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, a heterocyclic ring, C_7 to C_{12} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, cyclic C_2 to C_7 alkylene, substituted cyclic C_2 to C_7 alkylene, cyclic C_2 to C_7 heteroalkylene,

substituted cyclic C_2 to C_7 heteroalkylene, carboxy, protected carboxy, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, C_1 to C_4 alkylthio, C_1 to C_4 alkylsulfonyl, C_1 to C_4 alkylsulfoxide, phenylthio, substituted phenylthio, phenylsulfoxide, substituted phenylsulfoxide, phenylsulfonyl and substituted phenylsulfonyl;

X is selected from the group consisting of hydroxy, amino, protected amino, (monosubstituted)amino, (disubstituted)amino, an amino acid, aniline, substituted aniline, a heterocyclic ring, an aminosubstituted heterocyclic ring, and a substituted aminosubstituted heterocyclic ring; and

Y is selected from the group consisting of CH_2NHR^7 and $C(O)NHR^7$, wherein R^7 is a hydrogen atom, C_1 to C_6 alkyl and C_1 to C_6 substituted alkyl.

64. The combinatorial library of claim 63, wherein:

R^1 is selected from the group consisting of C_1 to C_9 alkylene, C_1 to C_9 substituted alkylene and a group of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

wherein u is selected from a number 1 to 8; and R^8 is selected from the group consisting of a hydrogen atom, C_1 to C_9 alkyl, C_1 to C_9 substituted alkyl, C_7

to C_{12} phenylalkyl and C_7 to C_{12} substituted phenylalkyl.

65. The combinatorial library of claim 63, wherein:

R^2 is selected from the group consisting of phenyl, substituted phenyl, a heterocyclic ring, amino substituted heterocyclic ring and a substituted heterocyclic ring.

66. The combinatorial library of claim 63, wherein:

R^3, R^4, R^5 and R^6 are, independently, a hydrogen atom.

67. The combinatorial library of claim 63, wherein:

X is selected from the group consisting of hydroxy, amino, protected amino, (monosubstituted)amino, (disubstituted)amino, aniline, substituted aniline, a heterocyclic ring, a substituted heterocyclic ring, an aminosubstituted heterocyclic ring, and a substituted aminosubstituted heterocyclic ring.

68. The combinatorial library of claim 63, wherein:

Y is CH_2NHR^7, wherein R^7 is selected from the group consisting of a hydrogen atom, C_1 to C_6 alkyl and C_1 to C_6 substituted alkyl.

69. The combinatorial library of claim 63, wherein:

R^1 is selected from the group consisting of C_1 to C_9 alkylene, C_1 to C_9 substituted alkylene and a group of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

wherein u is selected from a number 1 to 8; and R^8 is selected from the group consisting of a hydrogen atom, C_1 to C_9 alkyl, C_1 to C_9 substituted alkyl, C_7 to C_{12} phenylalkyl and C_7 to C_{12} substituted phenylalkyl;

R^2 is selected from the group consisting of phenyl, substituted phenyl, a heterocyclic ring, amino substituted heterocyclic ring and a substituted heterocyclic ring;

R^3, R^4, R^5 and R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of hydroxy, amino, protected amino, (monosubstituted)amino, (disubstituted)amino, aniline, substituted aniline, a heterocyclic ring, a substituted heterocyclic ring, an aminosubstituted heterocyclic ring, and a substituted aminosubstituted heterocyclic ring; and

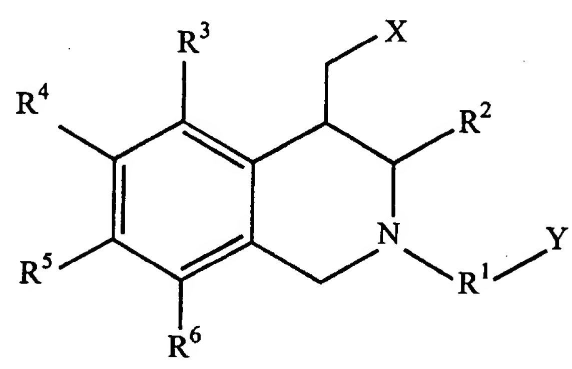
Y is CH_2NHR^7, wherein R^7 is selected from the group consisting of a hydrogen atom, C_1 to C_6 alkyl and C_1 to C_6 substituted alkyl.

70. A method of treating erectile dysfunction in a subject, comprising administering to the subject an effective amount of a melanocortin receptor ligand, wherein said melanocortin receptor ligand comprises the isoquinoline compound of claim 1.

71. A method of treating erectile dysfunction in a subject, comprising administering to the subject an effective amount of a melanocortin receptor ligand, wherein said melanocortin receptor ligand comprises the isoquinoline compound of claim 7.

72. A method of treating erectile dysfunction in a subject, comprising administering to the subject an effective amount of a melanocortin receptor ligand, wherein said melanocortin receptor ligand comprises the isoquinoline compound of claim 14.

73. The method of claim 72, wherein said melanocortin receptor ligand comprises an isoquinoline compound of the formula:



wherein:

R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 3; and R^8 is methyl; R^2 is 4-butylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2.

Fig. 1A

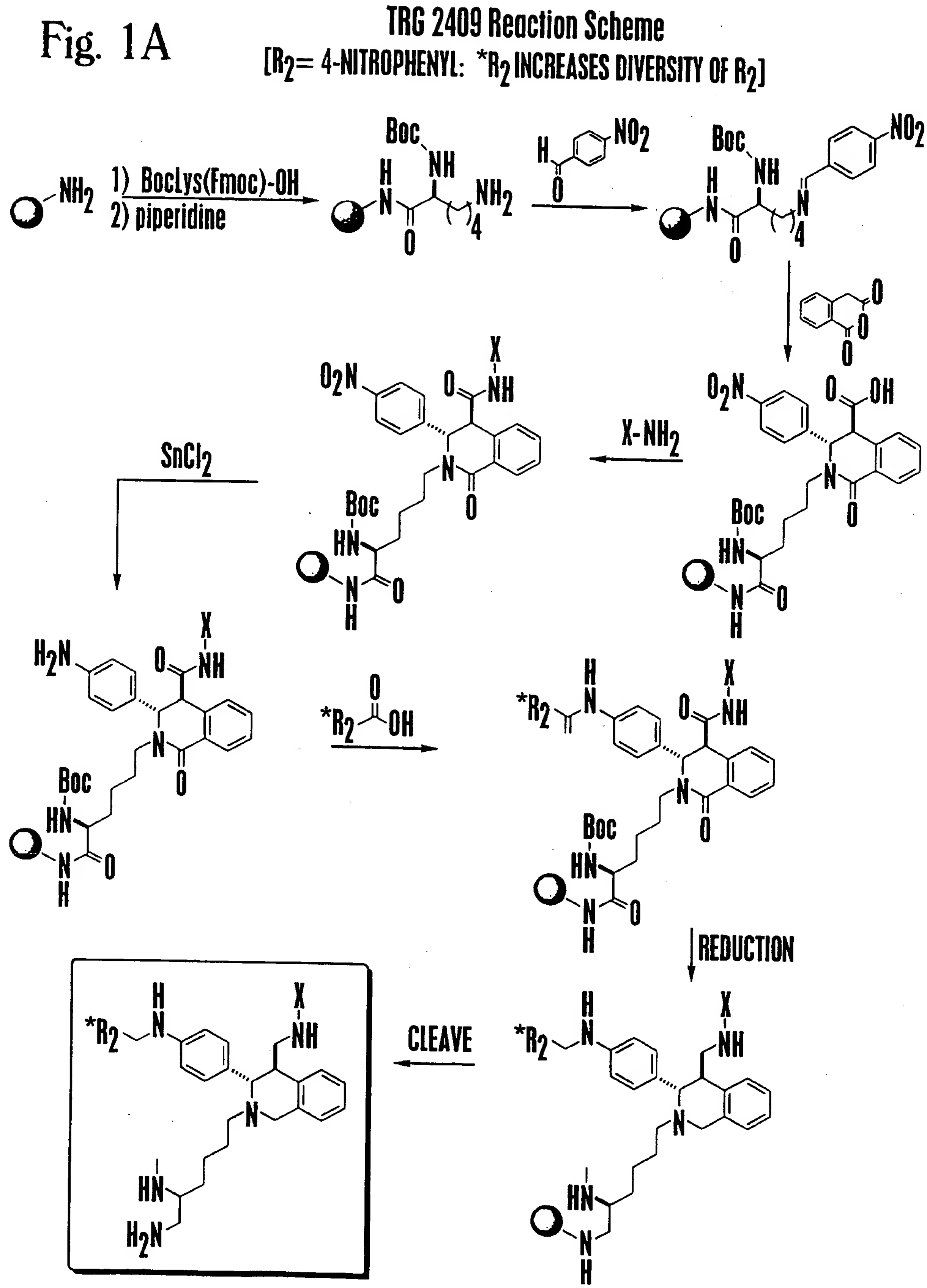

TRG 2409 Reaction Scheme
[R2= 4-NITROPHENYL: *R2 INCREASES DIVERSITY OF R2]
1) BocLys(Fmoc)-OH
2) piperidine
X-NH2
SnCl2
REDUCTION
CLEAVE

Fig. 1B TRG 2411 Reaction Scheme

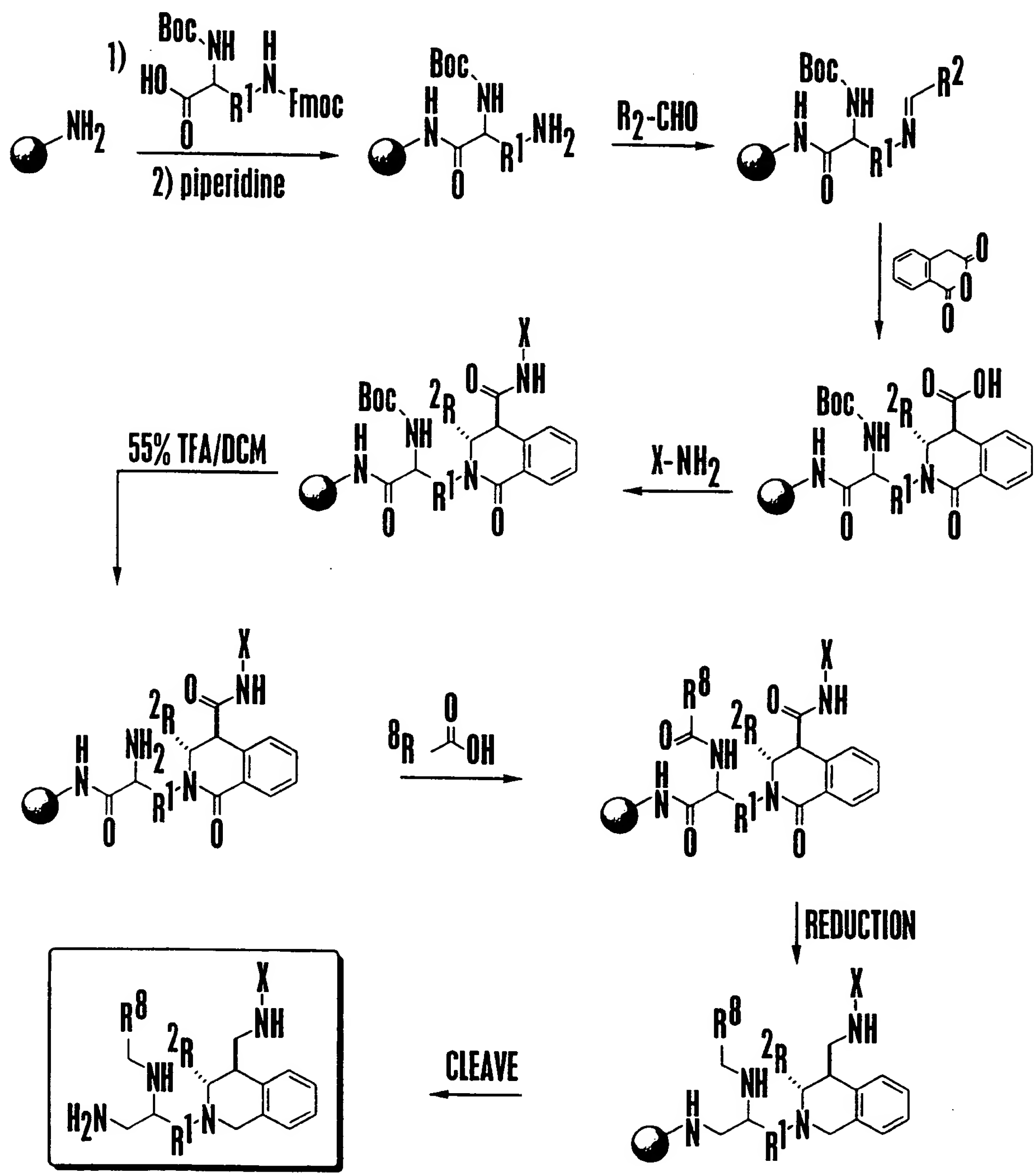


Fig. 2

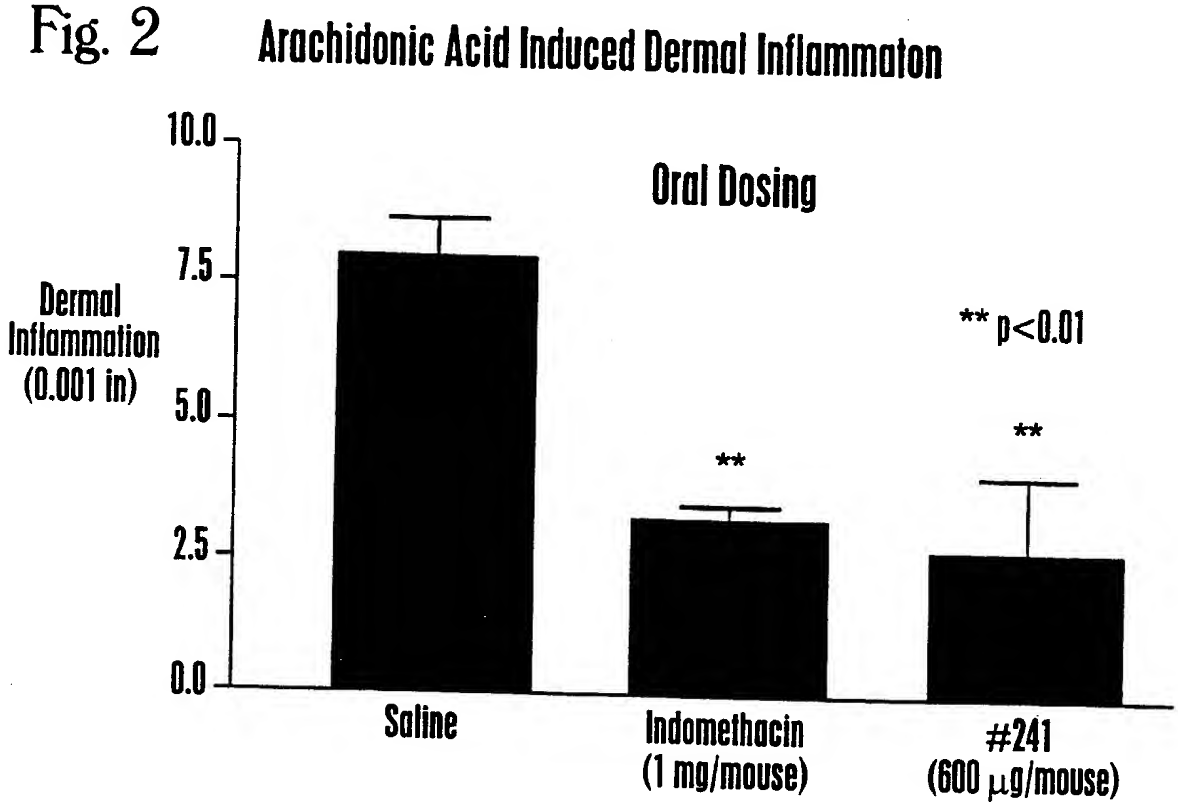

Arachidonic Acid Induced Dermal Inflammaton
Oral Dosing
Dermal Inflammation (0.001 in)
10.0
7.5
5.0
2.5
0.0
** p<0.01
**
**
Saline
Indomethacin (1 mg/mouse)
#241 (600 μg/mouse)

Fig. 3

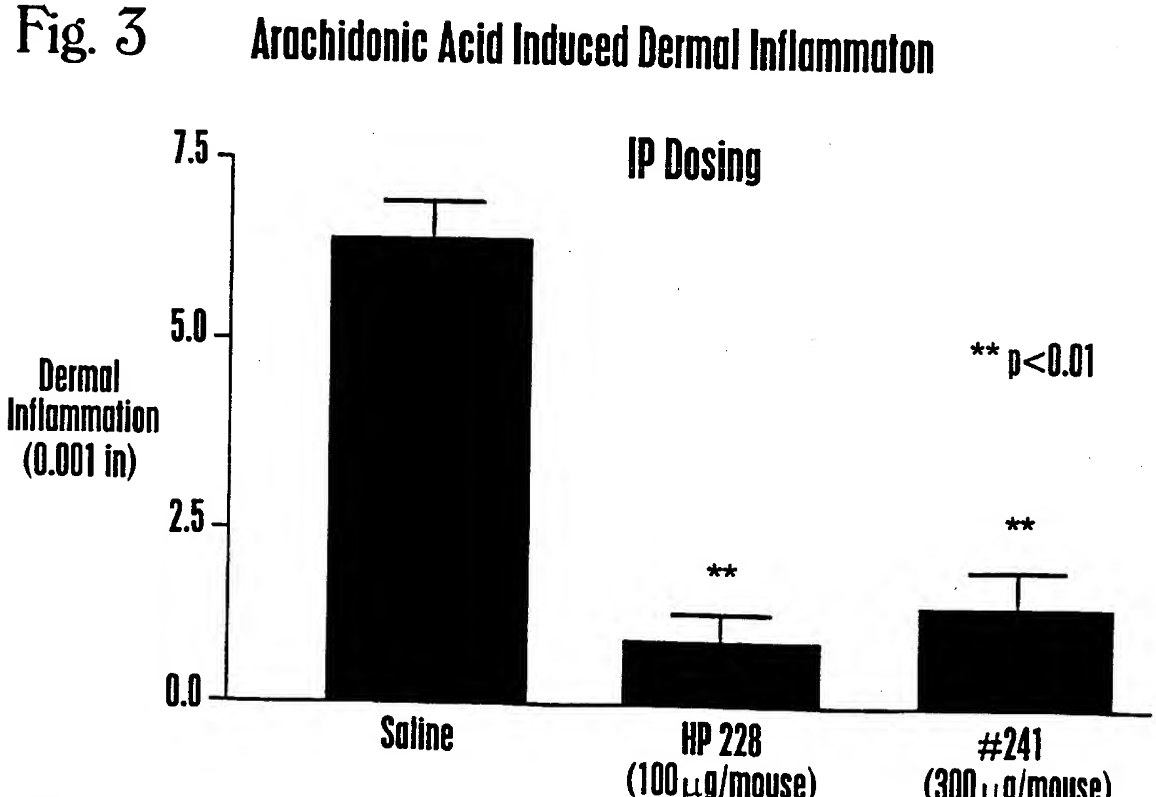

Arachidonic Acid Induced Dermal Inflammaton
IP Dosing
Dermal Inflammation (0.001 in)
7.5
5.0
2.5
0.0
** p<0.01
**
**
Saline
HP 228 (100μg/mouse)
#241 (300μg/mouse)

Fig. 4

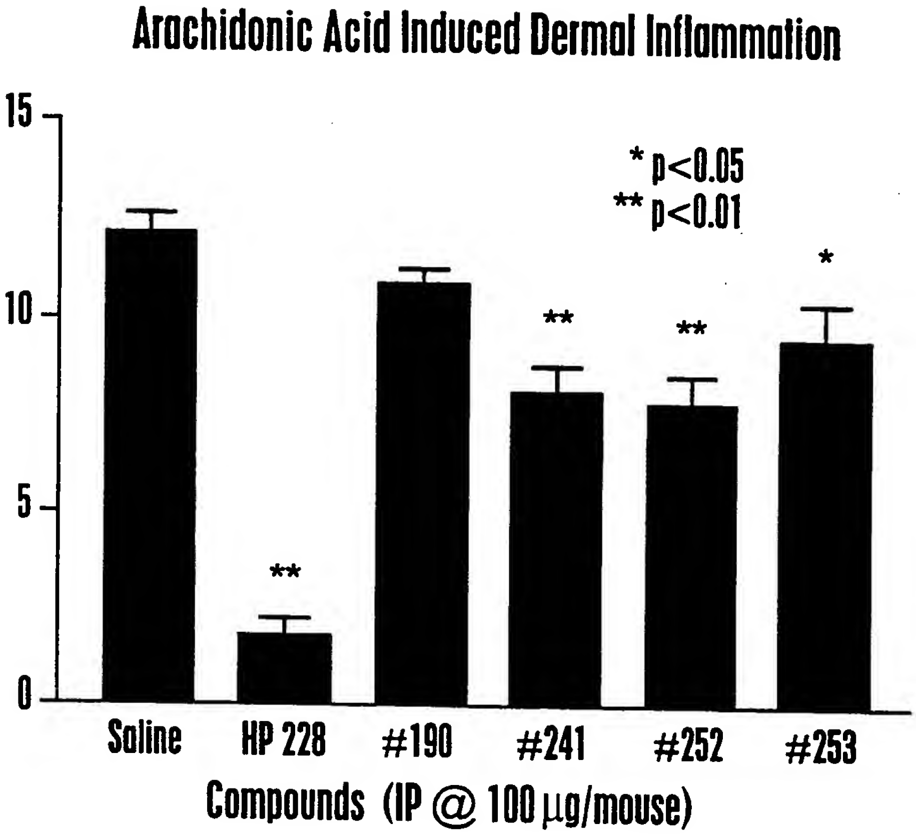

Arachidonic Acid Induced Dermal Inflammation
15
10
5
0
Dermal Inflammation (0.001 in)
* p<0.05
** p<0.01
**
*
**
**
Saline
HP 228
#190
#241
#252
#253
Compounds (IP @ 100 µg/mouse)

Fig. 5

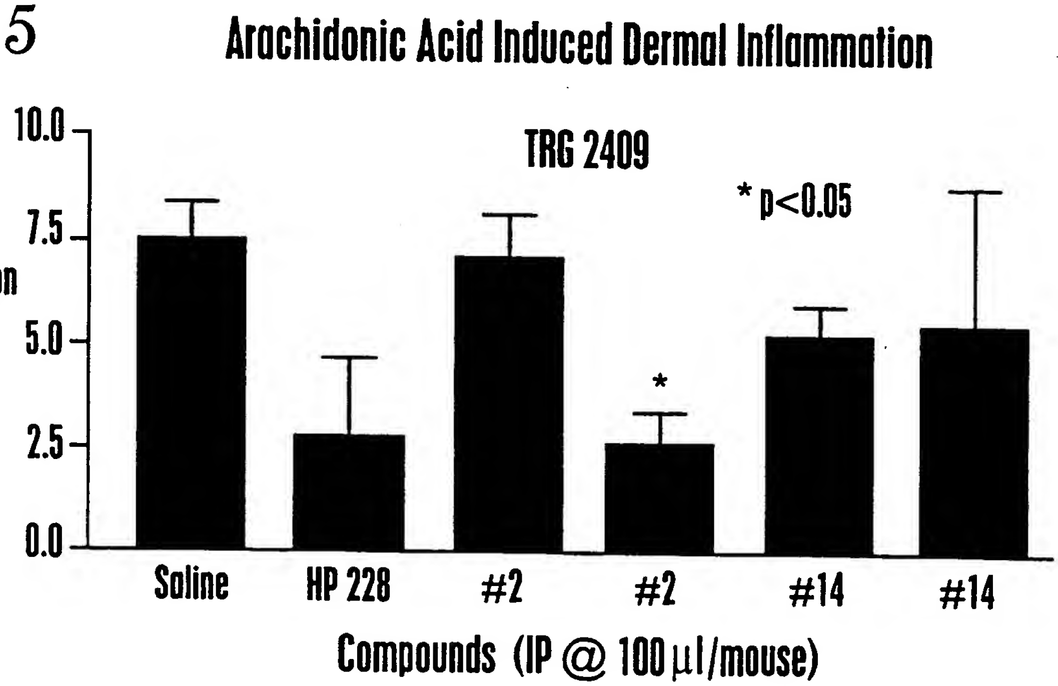

Arachidonic Acid Induced Dermal Inflammation
10.0
7.5
5.0
2.5
0.0
Dermal Inflammation (0.001 in)
TRG 2409
* p<0.05
*
Saline
HP 228
#2
#2
#14
#14
Compounds (IP @ 100 µl/mouse)

Fig. 6A

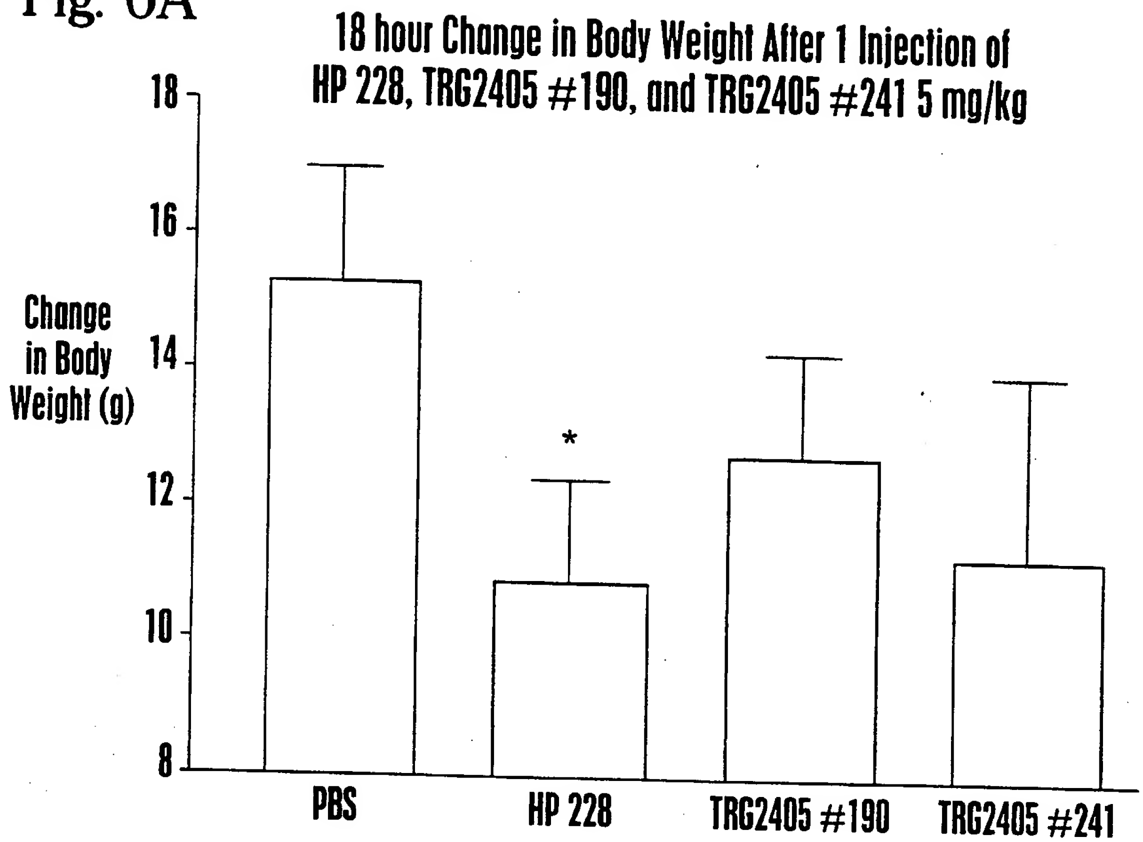

18 hour Change in Body Weight After 1 Injection of
HP 228, TRG2405 #190, and TRG2405 #241 5 mg/kg
Change in Body Weight (g)
18
16
14
12
10
8
*
PBS
HP 228
TRG2405 #190
TRG2405 #241

Fig. 6B

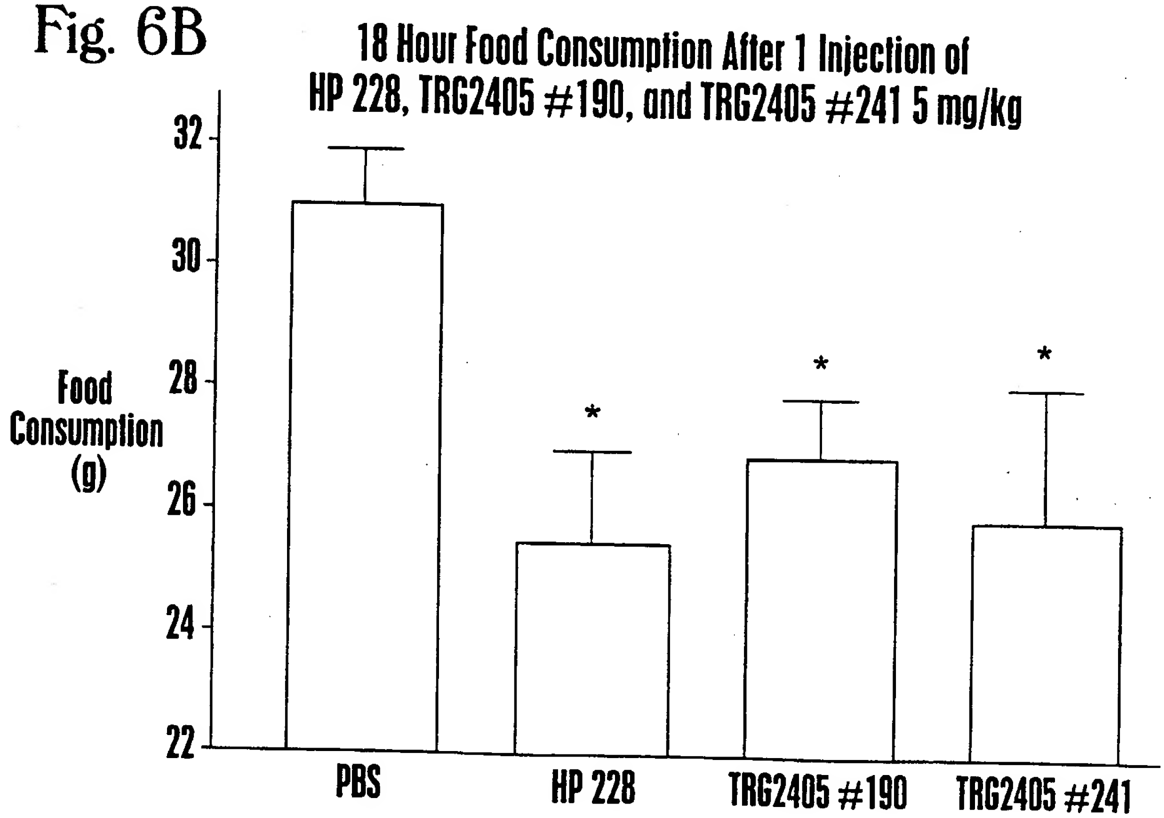

18 Hour Food Consumption After 1 Injection of
HP 228, TRG2405 #190, and TRG2405 #241 5 mg/kg
Food Consumption (g)
32
30
28
26
24
22
*
*
*
PBS
HP 228
TRG2405 #190
TRG2405 #241

Fig. 7A

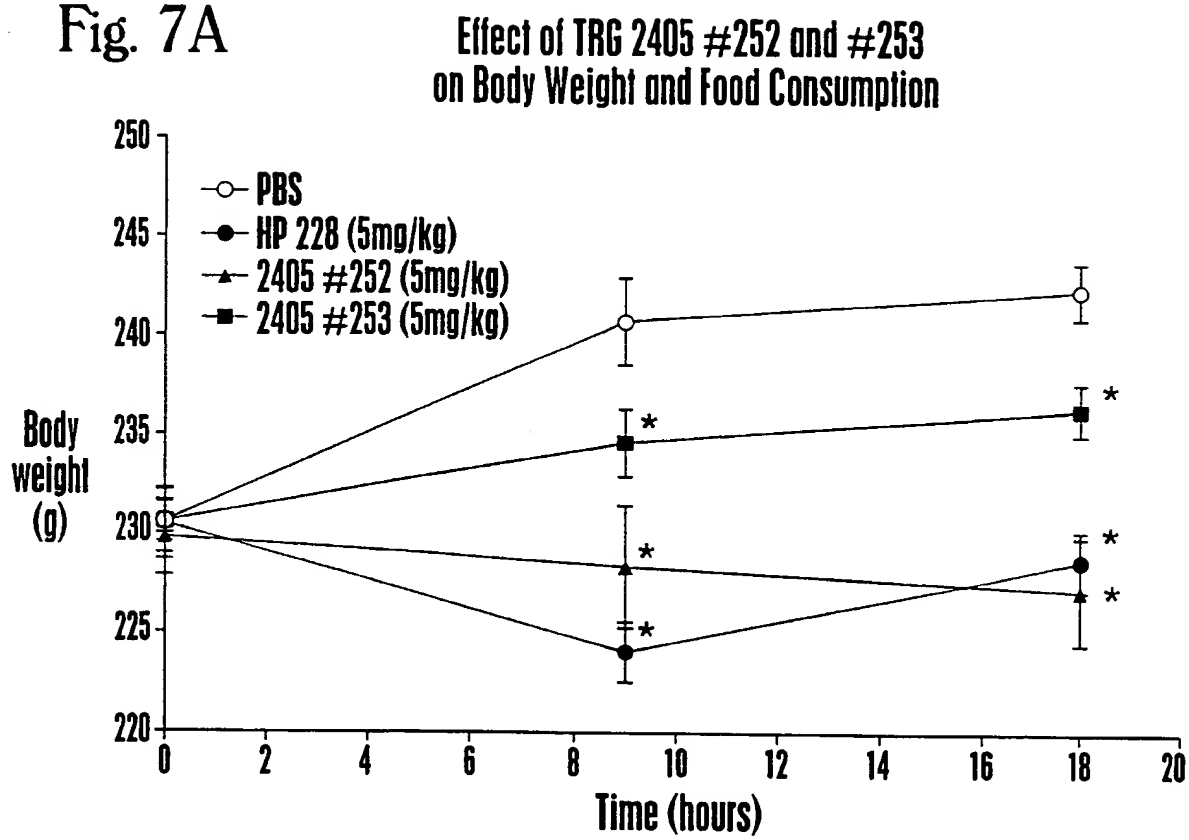

Effect of TRG 2405 #252 and #253
on Body Weight and Food Consumption
PBS
HP 228 (5mg/kg)
2405 #252 (5mg/kg)
2405 #253 (5mg/kg)
Body weight (g)
250
245
240
235
230
225
220
0
2
4
6
8
10
12
14
16
18
20
Time (hours)
*

Fig. 7B

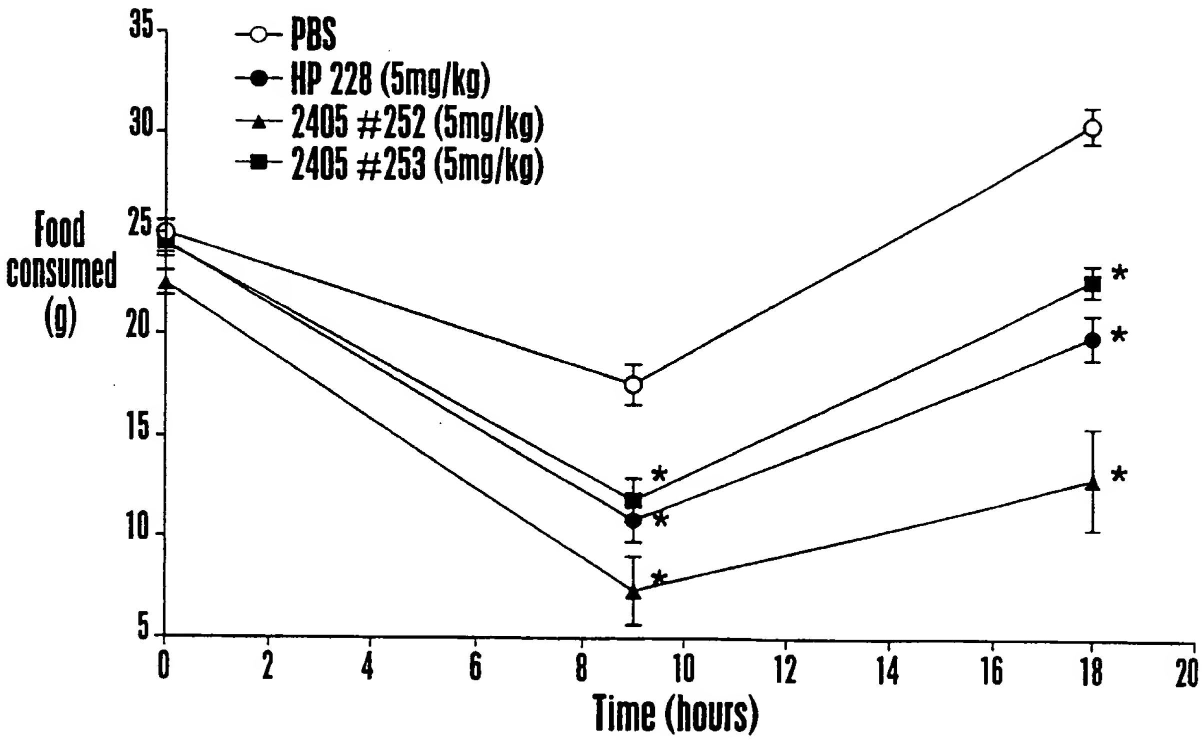

PBS
HP 228 (5mg/kg)
2405 #252 (5mg/kg)
2405 #253 (5mg/kg)
Food consumed (g)
35
30
25
20
15
10
5
0
2
4
6
8
10
12
14
16
18
20
Time (hours)
*

Fig. 8

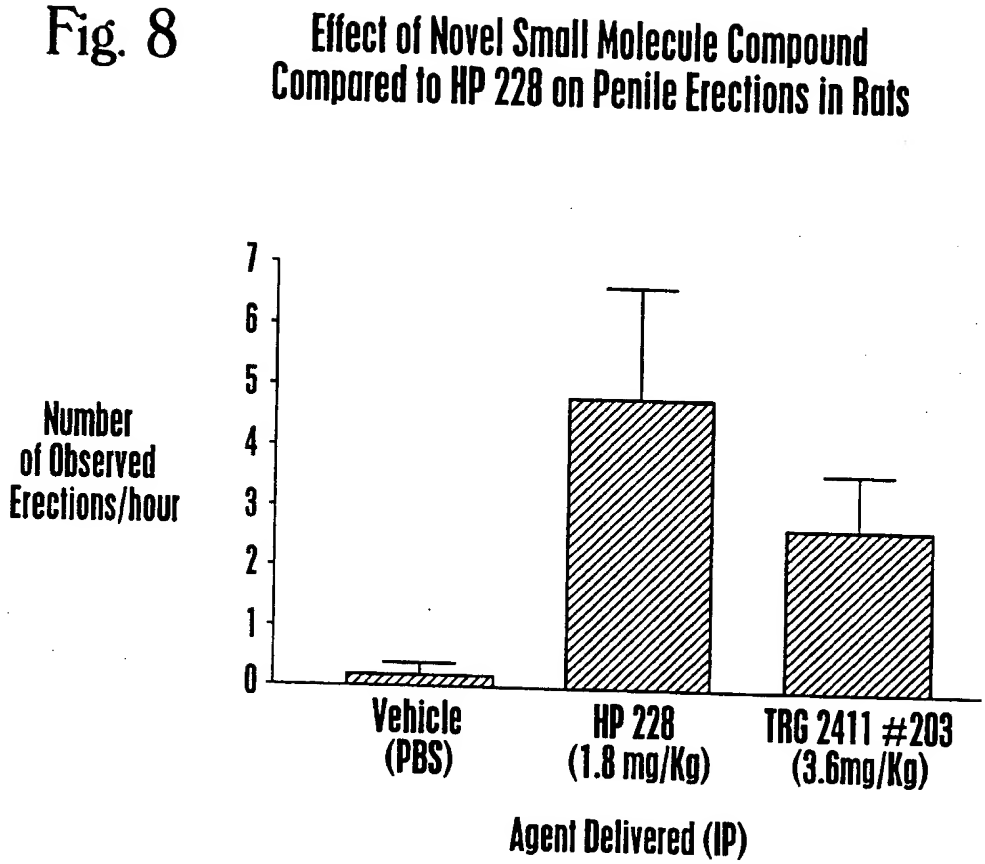
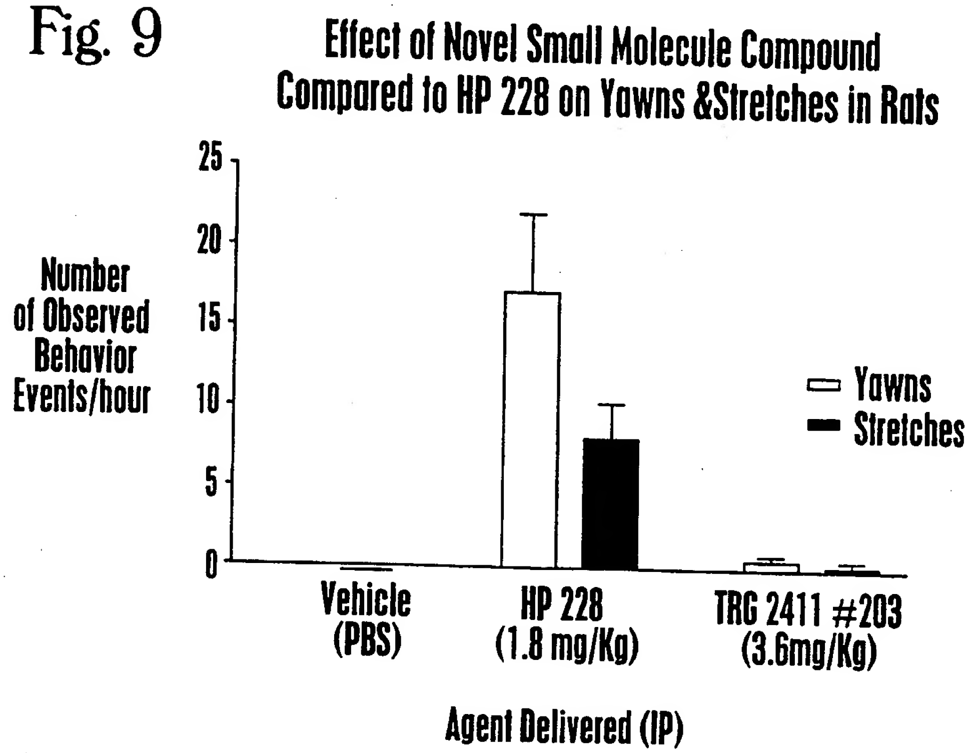

Effect of Novel Small Molecule Compound
Compared to HP 228 on Penile Erections in Rats
Number of Observed Erections/hour
7
6
5
4
3
2
1
0
Vehicle (PBS)
HP 228 (1.8 mg/Kg)
TRG 2411 #203 (3.6mg/Kg)
Agent Delivered (IP)

Fig. 9


Effect of Novel Small Molecule Compound
Compared to HP 228 on Yawns &Stretches in Rats
Number of Observed Behavior Events/hour
25
20
15
10
5
0
Yawns
Stretches
Vehicle (PBS)
HP 228 (1.8 mg/Kg)
TRG 2411 #203 (3.6mg/Kg)
Agent Delivered (IP)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/09216

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 217/04; A61K 31/47
US CL :514/307; 546/139, 146
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/307; 546/139, 146

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS COMPUTER SEARCH 1966-TO DATE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	US 5,874,443 A (KIELY et al) 23 February 1999, see entire document.	1-73
A	GALLOP et al. Application of Combinatorial Technologies to Drug Discovery. 1. Background and Peptide Combinatorial Libraries. 1994, Vol. 37, No. 9, pages 1233-1251.	1-73

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 JULY 1999	16 AUG 1999

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	ZINNA N. DAVIS Lawrence for
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

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